World Health Organization

SURVEY OF THE QUALITYOF SELECTED ANTIRETROVIRAL MEDICINES CIRCULATING IN FIVE AFRICAN COUNTRIES








2019

Survey of the quality of selected antiretroviral medicines circulating in five African countries

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Glossary of terms and abbreviations

Sample	for the purposes of this project means an item collected of a medicine's presentation (identified by the name, content of APIs, dosage form, strength, batch number and manufacturer) at a specific collection site. This means that a product with the same name, content of APIs, dosage form and strength, of the same batch produced by the same manufacturer, but collected at two different sites, represents two samples.
Procurement centre	for the purpose of this project means a point where a medicine enters the country, a central store and/or a store where a medicine is kept during in-country distribution.
Treatment centre	for the purpose of this project means the final site where a medicine is delivered and where it is provided to a patient.
Country codes	BF - Burkina Faso DRC - Democratic Republic of the Congo NG - Nigeria RW - Rwanda ZM - Zambia
Codes for medicines	EFV - efavirenz tablets TEE - efavirenz/emtricitabine/tenofovir disoproxil fumarate tablets LAT - lamivudine tablets LNZ - lamivudine/nevirapine/zidovudine tablets LZT - lamivudine/zidovudine tablets NEV - nevirapine tablets
AIDS	Acquired immune deficiency syndrome
API	Active pharmaceutical ingredient
ARV	Antiretroviral
BP	British Pharmacopoeia
DR Congo	Democratic Republic of the Congo
FDC	Fixed-dose combination
GMP	Good manufacturing practice
HIV	Human immunodeficiency virus
HPLC	High performance liquid chromatography
INN	International Nonproprietary Names for pharmaceutical substances
NGO	Non-governmental organization
NLT	Not less than
NMRA	National medicines regulatory authority
NMT	Not more than
Ph. Int.	*The International Pharmacopoeia*
PMS	Post-market surveillance
QCL	Quality control laboratory
U.S.	United States
U.S. FDA	U.S. Food and Drug Administration
USP	United States Pharmacopeia
WHO	World Health Organization
WHO-PQ	WHO Prequalification Team

Executive summary

- The main objective of the survey was to assess the quality of selected WHO prequalified antiretroviral medicines (ARVs) obtained at approved (authorized/accredited) public and private sector procurement and treatment sites.
- Although ARVs with a higher probability of substandard quality were targeted, the collected samples proved to be of good quality.
- The results of the current study, compared with those of a study organized by WHO-PQ in 2007, demonstrate that the quality of prequalified products remained very high: the failure rate decreased from 1.8% to 0.8%, the share of prequalified products among those found on the market and sampled increased from 53% to 98%.
- Repeatedly documented zero failure rates for prequalified products demonstrates that WHO prequalification reliably assures compliance with uniform quality standards.
- Participating countries valued the survey benefits of capacity building in market surveillance and recommended that future surveys should also include point-of-collection sample screening before submission of samples to designated laboratories for testing. In addition, parallel in-country testing of samples in national quality control laboratories as an element of proficiency testing, capacity and confidence building was recommended. WHO was also urged to explore development of data-sharing platforms or repositories of in-country testing results

The survey was organized by the WHO Prequalification Team (WHO-PQ) in cooperation with the national medicines regulatory authorities/ministries of health in five Sub-Saharan African countries of Burkina Faso, Democratic Republic of the Congo (DR Congo), Nigeria, Rwanda and Zambia. **The main objective of the survey was to assess the quality of selected WHO prequalified antiretroviral medicines (ARVs) obtained at approved (authorized/accredited) public and private sector procurement and treatment sites.** Samples were collected by the respective national authorities in each country focusing on fixed-dose combinations and paediatric formulations.

Quality testing was conducted according to official pharmacopoeias (The International Pharmacopoeia, the British Pharmacopoeia and the United States Pharmacopeia), as applicable, to facilitate comparison of products from different manufacturers by applying the monograph for all. As this survey was organized by WHO-PQ, whenever a prequalified product was found to be out of specification, the validated method accepted within the prequalification procedure was used for retesting and the statement of compliance based on the retesting.

A total of 126 samples of the following medicines were collected and tested:

- efavirenz 600 mg tablets
- efavirenz/emtricitabine/tenofovir disoproxil fumarate 600/200/300 mg tablets
- lamivudine 150 mg tablets
- lamivudine/nevirapine/zidovudine 30/50/60 mg dispersible tablets
- lamivudine/nevirapine/zidovudine 150/200/300 mg tablets
- lamivudine/zidovudine 30/60 mg dispersible tablets
- lamivudine/zidovudine 30/60 mg tablets
- lamivudine/zidovudine 150/300 mg tablets
- nevirapine 50 mg dispersible tablets.

The survey was conducted following a pre-established protocol and sampling was conducted over three months. **No samples were collected from the informal non-regulated market.** The outcomes of the survey therefore relate to a limited set of countries, a specific selection of medicines and a limited number of samples.

Each manufacturer was requested to confirm manufacture of the sampled batches including expiry dates and manufacturing site, minimizing the risk of inclusion of falsified products among the samples. Although ARVs with a higher probability of substandard quality were targeted, the collected samples proved to be of good quality. The pharmacopoeial and manufacturers' methods and specifications used in the survey did not identify any apparent quality problems, with the exception of an issue relating to the appearance of one sample. Given the absence of negative results, detailed analysis of potential quality deficiencies was not possible.

However, interesting observations were made. In the majority of cases pharmacopoeial monographs were sufficient to properly control products. But in two products tested they provided marginally failing results, even though retesting using the validated and WHO PQ-accepted manufacturers' methods had produced positive results.

The results of the current study, compared with those of a study organized by WHO-PQ in 2007, demonstrate that the quality of prequalified products remained very high. **The failure rate decreased from 1.8% to 0.8%. The share of prequalified products among those found on the market and sampled increased from 53% to 98%. Repeatedly documented zero failure rates for prequalified products demonstrates that WHO prequalification reliably assures compliance with uniform quality standards.**

All collected products were produced by eight Indian manufacturers, with no representation of local production. The complexity of procurement and distribution of ARVs was underscored by the fact that some of the manufacturers did not know to which markets their products were finally supplied; re-distribution of medicines among countries was frequent.

The availability of certain medicines selected for the survey was influenced by local therapeutic guidelines and practices. Although rigorous registration practices are implemented in several participating countries, other mechanisms described in local legislation, that bypass normal registration processes, were also used to ensure a continued supply of needed medicines. The survey did not evaluate to what extent these mechanisms rely on assessment and inspection performed by other parties, such as WHO or U.S. FDA, or whether the selected ARVs were approved and imported fully in line with prequalified conditions, *e.g.* through the WHO collaborative registration procedure. Four of the survey countries (Burkina Faso, DR Congo, Nigeria and Zambia) were participating in the WHO collaborative registration procedure at the time of the survey. However, at the time of sample collection only Nigeria had registered products via this procedure.

The survey indicated that storage conditions in procurement and treatment centres in participating countries adhere to good practices and therefore had not impacted negatively on the quality of the samples studied.

In discussions following conclusion of the survey, participating countries appreciated the survey benefits of capacity building in market surveillance and recommended that future surveys should also include point-of-collection sample screening before submission of samples to designated laboratories for testing. In addition, parallel in-country testing of samples in national quality control laboratories as an element of proficiency testing, capacity and confidence building was recommended. WHO was also urged to explore development of data-sharing platforms or repositories of in-country testing results.

1 Introduction

1.1 Background

In 2015 there were 2.1 million new HIV infections worldwide, adding up to a total of 36.7 million people living with HIV [1]. A lot of effort and finance have been expended on trying to optimize treatment and improving access to treatment modalities. In just two years (2014 and 2015) the number of people living with HIV on antiretroviral therapy increased by about a third, reaching 17.0 million people – 2 million more than the "15 million by 2015" target set by the United Nations General Assembly in 2011. Since the first global treatment target was set in 2003, annual AIDS-related deaths have decreased by 43%. In the world's most affected region of eastern and southern Africa, the number of people on treatment has more than doubled since 2010, reaching nearly 10.3 million people. AIDS-related deaths in the region have decreased by 36% since 2010 [1].

However, investment into treatment is lost if the medicines that the patients take are of poor quality since it is linked to their safety and effectiveness. Unfortunately, not all countries have sufficiently stringent systems of medicines regulation in place to ensure that only medicines of good quality are available to patients. According to World Health Organization (WHO) internal baseline estimates, only 56 of 194 Member States (28%) have national medicines regulatory authorities (NMRAs) with minimal or functional capacity to regulate vaccines and medicines. NMRAs in low-income countries often lack sufficient financial and human resources to carry out controls in a stringent and comprehensive way. Most of these countries are recipients of donor-supported public financing for pharmaceutical supplies.

To assist procurers and NMRAs the WHO Prequalification Programme (WHO-PQ) was set up in 2001 as a service provided by WHO to facilitate access to medicines that meet unified standards of quality, safety and efficacy. The primary focus is on medicines for HIV/AIDS, malaria, tuberculosis, and reproductive health. From the outset, the programme was supported by UNAIDS, UNICEF, UNFPA and the World Bank as a concrete contribution to the United Nations' priority goal of addressing widespread diseases in countries with limited access to quality medicines. Medicines to treat HIV/AIDS are the most represented in the list of WHO-prequalified medicines/finished pharmaceutical products (337 of 532 at the time of writing this report).[1] WHO-PQ is also organizing surveys to monitor the quality of medicines (both WHO-prequalified and non-WHO-prequalified medicines) procured by UN agencies. These surveys are intended to contribute to national quality control of medicines, strengthening of health systems in countries and capacity building at NMRAs.

In the last WHO-coordinated quality survey of 2007 focusing on antiretroviral medicines [2] none of the products sampled in seven African countries[2] had any critical quality deficiencies that would pose serious risk to patients. Among the 394 samples collected, the overall failure rate was 1.8%. The content of active pharmaceutical ingredient of one sample exceeded the upper limit. One of 163 samples tested for disintegration failed to disintegrate completely within 30 minutes, and two of 153 samples tested for dissolution showed lower results than required. Fifty-three percent of sampled products were WHO-prequalified and all complied with specifications. Information on registration by NMRAs was available for 285 products; 84% of these were registered. Products not registered at the time of sampling were found in three countries, mostly at private sector facilities, and constituted 12% of the total of 394 sampled products. Since the survey was limited to official distribution points and treatment centres around the capital cities, the results should not be generalized to the entire territories of the countries surveyed.

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1 Source: WHO list of prequalified medicines/finished pharmaceutical products https://extranet.who.int/prequal/content/prequalified-lists/medicines), as at 24 March 2017.

2 Cameroon, Democratic Republic of the Congo, Kenya, Nigeria, United Republic of Tanzania, Uganda and Zambia, and a follow-up study was considered in further countries.

Since 2007 WHO-PQ has organized several medicines quality surveys focusing on antiretrovirals [2], antimalarial [3], anti-tuberculosis medicines [4], and reproductive, maternal, newborn and child health medicines [5]. During these studies the results, possible regulatory actions and possible ways to improve the situation were discussed with representatives of NMRAs from participating countries. Following the discussions a number of recommendations on corrective and preventative actions were made and included the following.

- Collaboration among NMRAs should be promoted with the objectives of exchanging information on substandard and falsified products circulating in markets, registered products, inspection outcomes, post-marketing surveillance (PMS) plans and outcomes of PMS activities. It was noted that collaboration is facilitated by harmonization of registration requirements and regulations on Good Manufacturing Practices (GMP) and PMS activities.

- Regulatory supervision of local manufacturers should be strengthened focusing on GMP compliance, including investigation of defects with manufacturers and follow-up of corrective and preventative actions.

- NMRAs should have PMS strategies which should serve as a basis for the development of PMS plans to verify medicines quality and organize PMS studies (*i.e.* sampling and laboratory testing). Planning of such studies should be based on an assessment of risks related to substandard quality, and should take into account signals on substandard quality, findings from inspections, and information from pharmacovigilance systems.

- NMRAs should identify registered products that are considered to be of acceptable standard for other countries, and be ready to share up-to date assessment and/or inspection reports with other regulators.

- NMRAs should identify products with pending applications for registration and products which are placed on the market using special mechanisms (donations, special imports, conditional approvals, specific treatment programmes etc.), and should consider arrangements for their registration and availability under regular regulatory oversight.

- Countries should apply innovative regulatory pathways to make those products available more quickly for which there are currently limited sources only – *e.g.* by using assessment and inspection reports of other regulators to accelerate decision-making processes – and apply different models of collaborative registration.

The current study was organized by WHO-PQ in order to continue monitoring the quality of prequalified ARVs. Although its sampling design is not consistent with those of previous studies, this study aimed also to evaluate whether any changes or trends could be identified.

Unlike previous studies, this study also included a review of some aspects of product information that accompanied the products and/or was available for health professionals and patients. The outcomes and evaluation of this review will be published in a separate report.

Testing of medicines in this study was performed by quality control laboratories (QCL) which meet WHO-recommended standards and have been prequalified by WHO. The aim of WHO prequalification of QCLs is to increase the range of quality control laboratories for which the acceptability for use by United Nations agencies has been proven. Participation in surveys such as this one represents an opportunity for WHO to evaluate some aspects of the quality of service of prequalified QCLs that are not regularly used by UN agencies.

1.2 Objectives of the survey

The primary objective of this study was to assess the quality of selected antiretrovirals obtained at approved (authorized/accredited) public and private sector procurement and treatment sites in selected countries, using laboratory tests to evaluate products against quality criteria. The following specific questions were addressed:

- What proportion of ARV medicines samples collected at procurement and treatment centres approved by local authorities fails quality testing?
- Which specific quality tests do the samples fail, if any?
- Are any of the deficiencies critical, *i.e.* could they substantially affect treatment efficiency and/or cause harm to the patient?
- In those countries included in the 2007 study, are there any noticeable trends in changes in medicine quality?
- Where poor quality medicines are detected, through what supply chains are they likely to be distributed and which market segments do they serve?
- How does the proportion of poor quality medicines vary at different levels of the regulated distribution chains?
- How does the proportion of poor quality medicines vary depending on the origin of medicines (locally produced versus imported from different countries)?
- Does the proportion of poor quality medicines vary depending on their registration status?
- What proportion of prequalified products is available at the various distribution levels and what is their quality?

The results of this survey are expected to assist responsible authorities in the surveyed countries to evaluate their markets and propose possible strategies and implementation plans to address any problems identified. This study also aims to help to build capacity among NMRA staff to coordinate post-market quality surveillance activities.

Product inserts (leaflets) were collected together with the samples. In each ARV treatment centre, at least one treatment staff (physician/ health officer/ nursing) and one dispensing staff (pharmacist/ druggist) were interviewed regarding product information and access to information sources. The questionnaires shown in Annexes 4A and 4B to the Survey protocol (Appendix 1) were used for this purpose. The information collected will be reviewed for compliance with local registration requirements, WHO prequalification (medicines) requirements and other WHO requirements in a separate study. This separate study will evaluate the quality of product information that is available for the health professionals distributing or dispensing the products, as well as the use of the information that is available on the WHO prequalification website on prequalified products.

Information gathered on the capacity and performance of the prequalified laboratories that did testing within this survey will be used for the evaluation of laboratories within the prequalification procedure.

Limitations of the survey

Due to time and resource constraints samples were collected in a limited number of regions, and only at approved procurement and treatment sites. The informal non-regulated market was not covered, as

in the countries surveyed the vast majority of antiretrovirals are provided to patients in treatment programmes free of charge, and therefore the informal market with antiretrovirals is expected to be negligible or non-existent. Nevertheless, the survey cannot claim to fully evaluate the quality of the target medicines throughout the distribution chain or the overall risk of patients' exposure to substandard medicines.

The study is a snapshot of the medicine quality situation in the official markets where samples were collected, and therefore has some important limitations in making conclusions. As is common for testing surveys, the findings of this survey are relevant only to the samples tested. Extrapolation to other batches not tested (or even within a tested batch) has limited validity as this would require evaluation of manufacturers' GMP compliance and assessment of product dossiers not available to WHO PQ (medicines).

The tests conducted cannot completely identify problems of bioavailability, if they exist.

Since the sampling design was not fully consistent with that of the previous ARV study (in which different ARV medicines were selected, and samples collected in and around capital cities only), there is only limited possibility to compare outcomes and assess the effectiveness of corrective actions for those countries that were included in both surveys.

2 Methodology

The survey was conducted according to a common protocol (Appendix 1), which was developed in cooperation with participating countries.

2.1 Survey period

A preparatory meeting with the focal persons nominated by each participating country was held in Ouagadougou, Burkina Faso on 6-7 July 2015 to discuss the availability and potential quality of selected medicines in the participating countries, finalize the survey protocol and provide detailed instructions for collection and transportation of samples to testing laboratories.

Following the meeting samples of the selected medicines were collected in the three-month period from September to November 2015. The samples were sent to four preselected testing laboratories, and testing was performed between November 2015 and May 2016. Any non-compliant outcomes, including tentative ones, were immediately shared with the focal persons. The testing results were summarized and provided to the participating countries in March 2017. The outcomes of the survey were discussed and analysed by WHO-PQ together with the representatives of the participating countries at a meeting in Paris, France, in March 2017.

2.2 Selection of medicines for sampling and testing

Medicines that were supplied in 2013-2014 to recipient countries funded by a major donor partner, The Global Fund to Fight AIDS, Tuberculosis and Malaria, were the main target of the study (a list is provided in Appendix 1, Annex 1A). These medicines were expected to correspond to those that were not available in local supply and therefore more likely to have quality problems, because gaps in local supply are generally expected to fuel availability of substandard and falsified products. Secondly, there was also a reasonable chance to find prequalified products among Global Fund-financed medicines, as the Global Fund's quality assurance policy relies on WHO prequalification as a mechanism providing assurance of a stringent quality assessment.

WHO-prequalified products were at the forefront of the survey. In the past five years there has been a steady increase in prequalification of antiretroviral paediatric formulations. As these were not targeted in previous studies they were prioritized in the selection for this survey.

Information from the WHO team responsible for monitoring substandard and falsified products[3] was also used in priority-setting. Current records show that about 50 prequalified products have been counterfeited to date. These include emtricitabine/ tenofovir disoproxil fumarate tablets, lopinavir/ ritonavir tablets and lamivudine/ nevirapine/ zidovudine tablets. However, not all of these could be included in the survey due to funding limitations and unavailability of pharmacopoeial reference monographs.

To optimize the use of resources available for this survey, a risk assessment (Appendix 1, Annex 1B) was performed on the products most commonly supplied in volume terms to various countries and regions. The following risk-based criteria were considered for selection of medicines for this survey:

[3] http://www.who.int/medicines/regulation/ssffc/surveillance/en/

Inclusion criteria

- Products at documented risk of inferior quality with actual or potential serious implications for patients and public health, e.g. due to treatment failures or use in large volumes;
- Medicines supplied by the Global Fund to 10 or more countries and supplied in large quantities in 2013-2014, so anticipated to be still available on the markets;
- Paediatric formulations;
- High probability of occurrence of a quality problem (taking into account complexity of manufacture, *e.g.* fixed-dose combinations (FDC) with 2 or more active ingredients; stability of product, *e.g.* susceptibility to quality deterioration due to unstable active pharmaceutical ingredients, liquid dosage forms; and suitability of specifications to control potential problems);
- Exposure of patients to the product (way of dispensing and extent of exposed population),
- Seriousness of potential harm (vulnerability of target population, risks related to product′s dosage form, route of administration and therapeutic properties, such as therapeutic index, risk of therapeutic failure, acute versus chronic use, development of resistance);
- Reported cases of substandard and falsified products; and/or
- Products with five or more prequalified generics, hence a potential for diversity on the market.

Exclusion criteria

- Products manufactured in countries with relatively stringent regulatory systems, hence deemed to be of assured quality;
- Products with no pharmacopoeial monographs, regardless of their prequalification status;
- Low risk products as evaluated in a risk assessment (Appendix 1, Annex 1B);
- Products supplied to a small number of countries (five or less) and in relatively low quantities;
- Products in bulk packaging for which transportation of samples would be costly, *e.g.* bottles; and/or
- Products with two or fewer prequalified generics, hence more reliance on innovator products.

The application of the selection criteria and outcomes of the risk assessment are outlined in annexes to the Survey protocol (Appendix 1, Annexes 1A and 1B). Taking into account the above considerations, and assuming that the majority of products supplied were prequalified, the following seven medicines were selected for sampling:

Monocomponent

- Efavirenz 600 mg tablets
- Lamivudine 150 mg or 300 mg tablets
- Nevirapine 50 mg dispersible tablets

Fixed-dose combination (FDC)

- Efavirenz/emtricitabine/tenofovir disoproxil fumarate 600/200/300 mg tablets
- Lamivudine/nevirapine/zidovudine 30/50/60 mg dispersible tablets
- Lamivudine/zidovudine 30/60 mg dispersible tablets
- Lamivudine/zidovudine 150/300 mg tablets

2.3 Participating countries

The following eight countries were approached with the request to participate and cooperate in the survey:

- Nigeria – included in the last WHO-coordinated ARVs survey in 2007;

- Vietnam – part of evaluation of the laboratory which is supplied with most of targeted products by donors;
- Zimbabwe – part of recently prequalified laboratory evaluation, and part of ZaZiBoNa[4] project;
- Democratic Republic of the Congo – included in the last WHO-coordinated ARVs survey in 2007;
- Zambia – included in the last WHO-coordinated ARVs survey in 2007, and part of ZaZiBoNa project;
- Burkina Faso – supplied with most of targeted products by donors and included in other non-ARV studies;
- Rwanda – recommended in the last WHO-coordinated ARVs survey in 2007 for a future study; and
- Senegal – recommended in the last WHO-coordinated ARVs survey in 2007 for a future study.

Based on the responses from countries and available resources the following five countries were included in this survey:

- Burkina Faso;
- Democratic Republic of the Congo;
- Nigeria;
- Rwanda; and
- Zambia.

NMRAs in each of the selected countries nominated a focal person for the survey to coordinate activities in the country. The responsibilities of the focal persons were as follows:

- Identify the appropriate sampling sites and expected availability of selected products;
- Prepare a national sampling plan;
- Organize sampling in the country and transportation of samples to the pre-specified testing laboratories,
- Participate in analysis of outcomes of quality monitoring of products and recommendation of corrective actions in the country, if necessary.

Appropriate arrangements were agreed with the NMRAs in the selected countries regarding cooperation, reimbursement of activities conducted by NMRAs and presentation of the results.

2.4 Selection of sample collection sites

In line with the study objectives samples were collected in public and private sector procurement and treatment sites approved by the authorities in selected countries. No samples were collected from the informal sector, *i.e.* outside the approved distribution system.

Sampling sites at first and second levels of the distribution chain were targeted, *i.e.* central medical stores, NGO central stores, warehouses of importers or major distributors or other facilities supplied directly within various programmes (the first level), as well as hospitals, treatment centres, pharmacies

[4] ZaZiBoNa Project – pilot project on work-sharing and joint medicine dossier review by four countries: Zambia, Zimbabwe, Botswana and Namibia. This project is supported by WHO-PQT, and the countries' involvement in this survey is expected to further improve the capacity of their regulatory staff to coordinate post-market quality surveillance. See http://www.mcaz.co.zw/index.php/latest-news/16-zazibona-collaborative-medicines-registration-process for more details.

and medical stores (the second level). The country teams were requested to collect approximately 40% of samples at first level facilities and 60% at second level facilities.

Two geographical regions in each country were to be targeted when selecting sampling sites for both distribution levels, preferably with equal distribution of sites between regions. The following guidance was provided for selection of geographical regions:

- Regions where more sites for sampling are available;
- Regions with at least one first level site;
- Regions with conditions (*e.g.* climatic, storage etc.) that are likely to affect the product; and/or
- Locations with likely presence of poor quality product.

Based on these criteria the focal persons in the selected countries identified the sample collection sites and prepared lists of products which were potentially available at these sites for the selected medicines. The lists and the approach to selection of sampling sites were discussed and agreed at the Ouagadougou meeting.

National sampling plans were developed by each focal person in cooperation with WHO-PQ according to the following instructions:

- Select two geographical regions;
- List all sites in the selected areas and select from them randomly seven sites; and
- Allocate medicines to be collected from each site.
- If during the sample collection it is established that not enough samples are available at the selected site, proceed to the next site specified on the list.

Detailed guidance was provided in the Survey protocol (Appendix 1).

2.5 Sample collection and transportation

For the purposes of this project, a sample means an item collected of a medicine's presentation (identified by the name, content of APIs, dosage form, strength, batch number and manufacturer) at a specific collection site. Therefore a product of the same name, content of APIs, the same dosage form, strength, batch number and from the same manufacturer collected at two different sites represents two samples.

Samples were collected by the staff of the NMRA in each participating country. Detailed national sampling plans were used, identifying the collection sites, medicines, number of batches and number of dosage units per sample to be collected (Appendix 1, Annex 2). The target number of samples to be collected in each country was set at 35, *i.e.* five samples for each of seven medicines. An exception was made in Burkina Faso where, due to the known unavailability of nevirapine 50 mg dispersible tablets, six samples of each of the other six medicines were to be collected. The collectors were asked to collect samples of products from various manufacturers rather than several batches produced by one manufacturer. If there were products available from many manufacturers per medicine, the collectors were instructed to choose those which in their opinion were the least quality-assured. Detailed instructions for collection and storage of samples were prepared (Appendix 1, Annex 2), and the focal persons arranged for training of collectors to familiarize them with the national sampling plan and instructions.

Collectors were required to be mindful of the stock of sampled products in treatment centres and to ensure that no shortages occurred as a result of sample collection. If needed, appropriate arrangements were to be made such as requesting replacements of medicines or payment for collected samples.

For each sample, the collectors assigned a unique code number and completed a standardized sample collection form (Appendix 1, Annex 3). The following details were recorded at the time of collection: product name, name of the API, dosage form, strength per unit dose, package size, type and material of primary container, batch number, date of manufacture, expiry date, name and address of manufacturer, quantity collected, registration status, site, date of sample collection, storage conditions at the site, and any observations made during collection. These details were considered essential not only to identify each sample and ensure its traceability but also for final data analysis.

Where a manufacturer's batch certificate of analysis was available for a samples collected, a copy was to be collected with the sample. At each sampling site the survey interview forms (Appendix 1, Annexes 4A and 4B) were completed and submitted to WHO-PQ.

The collected samples were required to be taken to NMRAs as quickly as possible and kept under controlled storage conditions, as per label requirements. The samples and their defined accompanying documents were sent to the respective assigned testing laboratories using courier services. Detailed instructions for dispatch of samples were provided in the survey protocol (Appendix 1, Sections 4.5 and 4.6).

2.6 Testing laboratories

Four WHO-prequalified quality control laboratories were selected for testing of samples collected within this survey: InphA GmbH – Institute for Pharmaceutical and Applied Analytics, Official Medicines Control Laboratory, Bremen, Germany; Medicines Control Authority of Zimbabwe, National Quality Control Laboratory, Harare, Zimbabwe; National Institute of Drug Quality Control, Hanoi, Viet Nam; and Tanzania Food and Drugs Authority, Quality Control Laboratory, Dar es Salaam, Tanzania. Table 1 shows the distribution of samples among the selected laboratories.

Table 1: Laboratories performing quality testing

Testing laboratory	Medicines tested
InphA GmbH Institute for Pharmaceutical and Applied Analytics, Official Medicines Control Laboratory, Bremen, Germany	Efavirenz/emtricitabine/tenofovir disoproxil fumarate 600/200/300 mg tablets
Medicines Control Authority of Zimbabwe, National Quality Control Laboratory, Harare, Zimbabwe	Lamivudine 150 mg or 300 mg tablets
National Institute of Drug Quality Control, Hanoi, Viet Nam	Lamivudine/nevirapine/zidovudine 30/50/60 mg dispersible tablets Lamivudine/nevirapine/zidovudine 150/200/300 mg tablets Nevirapine 50 mg dispersible tablets
Tanzania Food and Drugs Authority, Quality Control Laboratory, Dar es Salaam, Tanzania	Efavirenz 600 mg tablets Lamivudine/zidovudine 30/60 mg dispersible tablets Lamivudine/zidovudine 30/60 mg tablets Lamivudine/zidovudine 150/300 mg tablets

WHO-PQ covered all testing costs.

2.7 Quality tests conducted and test methods and specifications used

All medicines selected for this survey were in the form of tablets, either conventional or dispersible. For all samples collected the following tests were carried out:

- Appearance
- Identification
- Assay of each API
- Uniformity of dosage units - weight variation
- Dissolution

For samples in the form of dispersible tablets, disintegration test and test for fineness of dispersion were carried out. Taking into account established formulation and compatibility concerns and stability of active substances in the given dosage forms, and considering funds available for testing, the following tests were added:

- Tests for the impurity tenofovir monosoproxil and for water content for samples of efavirenz/ emtricitabine/tenofovir disoproxil fumarate tablets,
- Test for related substances for samples of lamivudine/ nevirapine/ zidovudine dispersible tablets.

For ease of testing of products from various manufacturers, the test methods and specifications used were those of the respective monographs from the British Pharmacopoeia 2015 (BP), *The International Pharmacopoeia* 5th Edition 2015 (Ph. Int.) or the United States Pharmacopeia 38 (USP) that were valid at the time of testing as detailed in Table 2 and in the testing protocol (Appendix 1, Annex 5). When a monograph for a particular medicine was available in more than one pharmacopoeia, the ability of the respective specifications and methods to reveal quality problems was considered and the monograph was selected accordingly. In some cases tests from several pharmacopoeias were used to provide a more complete picture of the quality of a particular medicine.

For lamivudine/ nevirapine/ zidovudine dispersible and conventional tablets the protocol envisaged dissolution test to be performed for nevirapine only according to the USP monograph for nevirapine tablets. However, as it is a fixed-dose combination of three APIs the application of the method for monocomponent product might pose problems. Therefore the dissolution test was performed according to the USP pending monograph for lamivudine, zidovudine and nevirapine tablets (draft 2—for public comment).[5] The acceptance criteria for dissolution of nevirapine were those stipulated in the USP monograph for nevirapine tablets.

Whenever a prequalified product was found to be out of specifications, the validated method accepted by WHO-PQ in the prequalification procedure was used for retesting.

[5] http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/pendingStandards/m1900.pdf; accessed 13 May 2015

Table 2: Tests conducted and methods and specifications applied for testing of selected medicines

Medicine	Tests	Specifications and methods
Efavirenz tablets	Appearance Identity Assay Weight variation Dissolution	USP monograph for efavirenz tablets
Efavirenz/emtricitabine/ tenofovir disoproxil fumarate tablets	Appearance Identity Assay Tenofovir monosoproxil-impurity Water content Weight variation Dissolution	Ph. Int. monograph for efavirenz, emtricitabine and tenofovir tablets
Lamivudine tablets	Appearance Identity Assay Weight variation Dissolution	BP monograph for lamivudine tablets
Lamivudine/nevirapine/ zidovudine dispersible tablets	Appearance Identity Assay Related substances Weight variation Dissolution of nevirapine Disintegration Fineness of dispersion	Ph. Int. monograph for zidovudine, lamivudine and nevirapine tablets + dissolution test according to USP pending monograph for lamivudine, zidovudine and nevirapine tablets (draft 2—for public comment)
Lamivudine/nevirapine/ zidovudine tablets	Appearance Identity Assay Weight variation Dissolution of nevirapine	Ph. Int. monograph for zidovudine, lamivudine and nevirapine tablets + dissolution test according to USP pending monograph for lamivudine, zidovudine and nevirapine tablets (draft 2—for public comment)
Lamivudine/zidovudine dispersible tablets	Appearance Identity Assay Weight variation Dissolution Disintegration Fineness of dispersion	BP monograph for zidovudine and lamivudine tablets
Lamivudine/zidovudine tablets	Appearance Identity Assay Weight variation Dissolution	BP monograph for zidovudine and lamivudine tablets
Nevirapine dispersible tablets	Appearance Identity Assay Weight variation Dissolution Disintegration Fineness of dispersion	USP monograph for nevirapine tablets

No specific tests were included to identify potential falsified products. However, for each sampled prequalified product a simple verification was made with the manufacturer stated on the label to confirm the authenticity of production details (batch number, dates of manufacture and expiry, manufacturing site and country of supply).

The following general specifications were used for evaluation of samples:

Appearance

Visual inspection was conducted according to the general monograph on Tablets in *The International Pharmacopoeia*.[6] Tablets should be undamaged, smooth, and usually of uniform colour. Presence of excessive powder and/or pieces of tablets in the container, cracks, chipping in the tablet surfaces or coating, swelling, mottling, discoloration, fusion between tablets, appearance of crystals on the container walls or on the tablets are signs of physical instability and are not acceptable.

Disintegration

The disintegration test was performed for dispersible tablets in line with the harmonized pharmacopoeial monograph, and the limit of not more than 3 minutes was applied.

Dissolution

Dissolution was tested in line with the harmonized pharmacopoeial monograph in three stages, with the following acceptance criteria:

Stage	Number of units tested	Acceptance criteria
S1	6 units	Each unit is not <Q*+5%
S2	Another 6 units	Average of 12 units (S1+S2) is ≥ Q, and no unit is <Q-15%
S3	Another 12 units	Average of 24 units (S1+S2+S3) is ≥Q, not more than 2 units are <Q-15%, and no unit is <Q-25%

*Q is the amount of dissolved active pharmaceutical ingredient specified in the individual monograph, expressed as a percentage of the content stated on the label. The testing is continued through the three stages unless the results conform at either stage 1 or stage 2.

Specifications applied in terms of Q values and testing time limits are shown in the testing protocol (Appendix 1, Annex 5).

Fineness of dispersion

Fineness of dispersion was tested according to the requirements of Ph. Eur. monograph for dispersible tablets. Two tablets were placed in 100 mL of water and stirred until completely dispersed. A smooth dispersion produced should pass through a sieve screen with a nominal mesh aperture of 710 µm (USP No. 25).

Uniformity of dosage units

The test for uniformity of dosage units was requested to be performed for all samples according to the USP monograph <905> Uniformity of dosage units - Weight variation (corresponding to Ph.Eur. 2.4.90 Uniformity of dosage units – Mass variation). One laboratory performed in addition the test according to Ph. Int. – Methods of analysis - 5.2 Uniformity of mass for single-dose preparations (corresponding to Ph. Eur. 2.4.5 Uniformity of mass of single-dose preparations). One laboratory performed only the test according to Ph. Int. For details see Appendices 3–8.

2.8 Compliance of samples with standards

The samples were considered to be in compliance with standards if they met the specifications set for this survey and outlined in the section above and/or listed in the respective tables of results in Appendices 3–8.

All results which were found out-of-specification were investigated, and tests were repeated as appropriate according to each laboratory's standard operating procedure on handling out-of-specification results.

In this survey all samples containing the same active pharmaceutical ingredient(s) in the same dosage form were tested according to the same specifications to enable comparison of samples from different manufacturers. It should be noted that individual manufacturers may use different specifications and different methods for testing of their products, and these specifications and methods may be approved by regulatory authorities in individual countries or within the WHO prequalification procedure. As this survey was organized by WHO-PQ, whenever a prequalified product was found to be out of specifications, the validated method accepted within the prequalification procedure was used for retesting and the statement of compliance was based on such retesting.

3 Results

3.1 Overview of samples collected

3.1.1 Medicines collected

A total of 126 samples were collected which represented 29 products[6] originating from eight pharmaceutical companies (manufacturers).[7] The breakdown of numbers of samples collected for individual medicines in individual countries, and numbers of manufacturers from which samples were collected in individual countries are shown in Table 3 (page 25).

Sample collectors adhered to the instructions and collected the requested products in the specified strengths and dosage forms. There were only two minor deviations:

- One sample of lamivudine/nevirapine/zidovudine 150/200/300 mg conventional tablets was collected in DR Congo instead of lamivudine/nevirapine/zidovudine 30/50/60 mg dispersible tablets,
- Five samples of lamivudine/zidovudine 30/60 mg conventional tablets in Nigeria and one sample of lamivudine/zidovudine 30/60 mg conventional tablets in Burkina Faso were collected instead of lamivudine/zidovudine 30/60 mg dispersible tablets.

Generally speaking there was limited availability of paediatric formulations.

3.1.2 Manufacturers and batches

The 126 samples tested in this survey represented 98 different batches and originated from a total of eight manufacturers, all based in India. The breakdown of collected samples according to their manufacturers is shown in Table 4 (page 26).

WHO-PQ contacted each of the manufacturers to ask for verification of the batch number, dates of manufacture and expiry, and manufacturing site of the collected samples, and for the information on destination countries and customers to which the respective product was supplied. The authenticity in terms of batch number, manufacturing and expiry dates, and manufacturing site was confirmed for all samples. Approximately 40% of samples were collected in countries other than those indicated as destination by the manufacturers. This potentially reflects centralized purchases of some medicines by international procurers, and onward distribution to other countries.

Twenty of the total 98 batches were sampled at two, three or four different sampling sites, mostly in the same country. There were three products for which samples of the same batch were collected in two different countries:

- Efavirenz 600 mg tablets, Strides Arcolab Ltd. India – the same batch was collected in Burkina Faso and Zambia;
- Lamivudine/ nevirapine/ zidovudine 30/50/60 mg dispersible tablets, Mylan Laboratories Ltd. India – the same batch was collected in DR Congo and Rwanda; and
- Lamivudine/ zidovudine 150/300 mg tablets, Hetero Labs Ltd India – the same batch was collected in DR Congo and Rwanda.

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[6] A product was identified by the name of manufacturer, dosage form and content of API(s) in qualitative and quantitative terms, *i.e.* various strengths were differentiated.

[7] A manufacturer was identified by the company name declared on the labelling, and the authenticity of each product was verified with individual manufacturers.

3.1.3 Sampling sites and storage conditions

A total of 45 collection sites in the five countries were included in the survey. Samples were collected in medical stores, stores of importers, hospitals, treatment centres and pharmacies. As requested by the survey protocol, sites were at the first (24%) and second (76%) level of distribution chain. It was found that 62% of the sites were in the public sector, 20% were NGO stores and 18% were in the private sector. The numbers of regions and sites where samples were collected in individual countries, with types of sites and numbers of collected samples, are shown in Table 5 (page 27). In Nigeria, the collectors visited 10 sites in total (6 in Lagos and 4 in Kaduna), however, due to unavailability of target medicines or for administrative reasons they were able to collect samples at six sites only. In other countries the collectors managed to collect some samples at each visited site.

The sample collectors were instructed to record on the sample collection forms the storage conditions at the sampling sites at the time of sample collection and provide the information whether the conditions were monitored and/or not controlled by the organization. For 113 samples the storage conditions were controlled with temperature recorded at the time of collection ranging from 17 - 31°C and relative humidity of 31–63%. For 13 samples the storage conditions were not monitored by the organization. Of these 13 samples, seven were however stored in air-conditioned storeroom (for two of these seven samples the recorded temperature was 18°C as measured by the sample collectors), four samples were stored at 32–39°C, and for two samples no information on temperature was provided in the sample collection form.

3.2 Registration status of sampled products

According to the information from national authorities in participating countries, overlay 49% of collected samples (62 of 126) represented products with a valid registration from the national regulatory body. However in the case of Nigeria all samples collected were registered. In Zambia for two samples the registration application was pending and the products had been supplied with special permission from the Ministry of Health. In Burkina Faso 64% of collected samples were of unregistered products supplied as donation or with a special permission. All samples collected in DR Congo and Rwanda were of unregistered products, which were supplied under a special permission from the Ministry of Health of the Democratic Republic of the Congo and as part of a central supply to government centres in Rwanda. In all cases the special permission was provided for in legislation.

Table 6 (page 28) shows the numbers of samples of registered and unregistered products by country, together with the mechanism of placing unregistered products on the market.

Table 3: Summary of samples collected in individual countries

Medicine	Burkina Faso		DR Congo		Nigeria		Rwanda		Zambia		Total	
	Number of samples	*Number of manufacturers*	**Number of samples**	*Number of manufacturers*	**Number of samples**	*Number of manufacturers*	**Number of samples**	*Number of manufacturers*	**Number of samples**	*Number of manufacturers*	**Number of samples**	*Number of manufacturers*
Efavirenz 600 mg tablets	**4**	*3*	**5**	*3*	**5**	*4*	**7**	*2*	**12**	*5*	**33**	*6*
Efavirenz/emtricitabine/ tenofovir disoproxil fumarate 600/200/300 mg tablets	**6**	*3*	no sample collected	*0*	no sample collected	*0*	no sample collected	*0*	**4**	*2*	**10**	*3*
Lamivudine 150 mg tablets	**3**	*2*	**3**	*2*	no sample collected	*0*	no sample collected	*0*	**5**	*2*	**11**	*5*
Lamivudine/nevirapine/ zidovudine 30/50/60 mg dispersible tablets	**2**	*1*	**4**	*1*	**5**	*2*	**5**	*2*	no sample collected	*0*	**16**	*3*
Lamivudine/nevirapine/ zidovudine 150/200/300 mg tablets	no sample collected	*0*	**1**	*1*	no sample collected	*0*	no sample collected	*0*	no sample collected	*0*	**1**	*1*
Lamivudine/zidovudine 30/60 mg dispersible tablets	**4**	*1*	**2**	*1*	no sample collected	*0*	**6**	*2*	**3**	*1*	**15**	*2*
Lamivudine/zidovudine 30/60 mg tablets	**1**	*1*	no sample collected	*0*	**5**	*1*	no sample collected	*0*	no sample collected	*0*	**6**	*1*
Lamivudine/zidovudine 150/300 mg tablets	**5**	*5*	**5**	*4*	**5**	*3*	**5**	*2*	**11**	*5*	**31**	*7*
Nevirapine 50 mg dispersible tablets	no sample collected	*0*	**3**	*1*	no sample collected	*0*	no sample collected	*0*	no sample collected	*0*	**3**	*1*
Total samples/overall manufacturers*, per country	**25**	*5*	**23**	*7*	**20**	*5*	**23**	*5*	**35**	*6*	**126**	*8*

* The overall number of manufacturers is less than the total of each column, as in some cases manufacturers were the same for different products

Table 4: Number of samples, by manufacturers

Medicine	**Auro-bindo Pharma**, India	**Cipla**, India	**Hetero Labs**, India	**Macleods Pharma-ceuticals**, India	**Micro Labs**, India	**Mylan Labora-tories**, India	**Ranbaxy Labora-tories**[a], India	**Strides Arcolab**, India	**Total samples**	*Number of products*
Efavirenz 600 mg tablets	2*	[3*]	[9*]	0	3	[6*]	0	[10*]	**33**	*6*
Efavirenz/emtricitabine/ tenofovir disoproxil fumarate 600/200/300 mg tablets	0	[4]	[2*]	0	0	[4]	0	0	**10**	*3*
Lamivudine 150 mg tablets	4*	[1]	[2*]	[2*]	[2]	0	0	0	**11**	*5*
Lamivudine/nevirapine/ zidovudine 30/50/60 mg dispersible tablets	0	2*	0	0	0	[12*]	0	[2]	**16**	*3*
Lamivudine/nevirapine/ zidovudine 150/200/300 mg tablets	0	0	0	0	0	[1*]	0	0	**1**	*1*
Lamivudine/zidovudine 30/60 mg dispersible tablets	0	9*	0	0	0	[6*]	0	0	**15**	*2*
Lamivudine/zidovudine 30/60 mg tablets	0	0	0	0	0	[6*]	0	0	**6**	*1*
Lamivudine/zidovudine 150/300 mg tablets	3*	[2*]	[12]	[1*]	0	[4*]	[5]	[4*]	**31**	*7*
Nevirapine 50 mg dispersible tablets	3*	0	0	0	0	0	0	0	**3**	*1*
Total samples	**12**	**21**	**25**	**3**	**5**	**39**	**5**	**16**	**126**	
Total products	*4*	*6*	*4*	*2*	*2*	*7*	*1*	*3*		*29*

[x] Product prequalified based on WHO-PQ assessment and inspection

x* Product on the prequalification list based on U.S. FDA approval

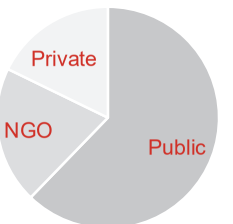
x Product not included in the WHO prequalification list.

a) Since 25 March 2015 Ranbaxy is operating under the amalgamated entity of Sun Pharmaceuticals Industries Ltd.

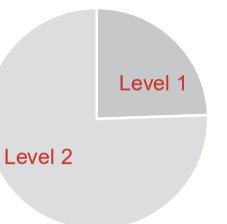
Table 5: Numbers of regions and collection sites in individual countries, with numbers of collected samples

Country	Number of regions	Number of sites	Public		NGO		Private		Level 1		Level 2	
			Number of sites	Number of samples	Number of sites	Number of samples	Number of sites	Number of samples	Number of sites	Number of samples	Number of sites	Number of samples
Burkina Faso	4	11	8	21	0	0	3	4	1	11	10	14
DR Congo	6	7	0	0	6	17	1	6	4	14	3	9
Nigeria	2	6	4	16	0	0	2	4	1	8	5	12
Rwanda	2	7	7	23	0	0	0	0	1	4	6	19
Zambia	6	14	9	23	3	8	2	4	4	12	10	23
Total	**20**	**45**	**28** (62%)	**83** (66%)	**9** (20%)	**25** (20%)	**8** (18%)	**18** (14%)	**11** (24%)	**49** (39%)	**34** (76%)	**77** (61%)
Grand total (sites)			**45** (100%)						**45** (100%)			
Grand total (samples)			**126** (100%)						**126** (100%)			

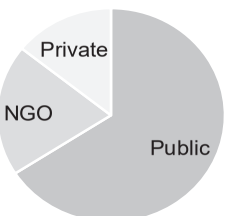
Sites:



Sites:



Samples:



Samples:

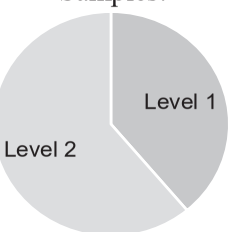


Table 6: Registration status of collected samples

Country	Total number of samples	Registered	Unregistered	Mechanism of placing unregistered medicines on the market
Burkina Faso	25	9	16	Donation or special permission
DR Congo	23	0	23	Special permission
Nigeria	20	20	0	Not applicable
Rwanda	23	0	23	Central supply to government centres
Zambia	35	33	2	Special permission of Ministry of health
Total	**126**	**62** (49%)	**64** (51%)	

3.3 WHO prequalification status of sampled products

Only selected medicines in specified formulations are invited for WHO prequalification.[8] The outcome of the prequalification procedure is the list of prequalified medicines/finished pharmaceutical products published by WHO.[9] The list contains products accepted after evaluation carried out by WHO-PQ, products accepted by other regulatory authorities that apply stringent standards for evaluation of quality, safety and efficacy similar to those recommended by WHO, such as the United States Food and Drug Administration (U.S. FDA), Health Canada and European Medicines Agency – can be co-listed with the WHO prequalified products. To a large extent products evaluated by WHO-PQ are also tentatively approved by U.S. FDA.

Only medicines invited for WHO prequalification at the time of the survey were included in this survey.

An overview of the prequalified products of which samples were collected in this survey, together with the information published by WHO-PQ on its website, is provided in Appendix 2 (and see also Table 4).

Of 126 samples collected:

- 100 samples (79.4%) represented products that were prequalified by WHO-PQ (22 products, 15 of them were also tentatively approved by U.S. FDA),
- 23 samples (18.2%) represented products listed based on a tentative approval by U.S. FDA (6 products), and
- Three samples (2.4%) represented one product which was not on the WHO prequalification list.

It was not established in all cases whether products were supplied to procurers and countries with claims for prequalification or not.

[8] https://extranet.who.int/prequal/
[9] https://extranet.who.int/prequal/content/prequalified-lists/medicines

3.4 Conformity of manufacturing sites, packaging, appearance and shelf life of collected samples with prequalification

For collected samples of prequalified products the conformity of manufacturing sites specified on labels, the packaging, appearance of dosage unit and shelf life was checked against the information published in the WHO list of prequalified medicines/finished pharmaceutical products and WHO Public Assessment Reports.[10] For products prequalified on the basis of evaluation carried out by WHO-PQ, full information on manufacturing sites, packaging, appearance of products and shelf life is available on the WHO PQ website. For products listed based on a tentative approval by U.S. FDA, only details of packaging are specified in the list and for some products also the manufacturing sites are identified. As no assessment reports are published for these products, appearance and shelf-life could not be checked.

Manufacturing sites

For all 100 samples of products prequalified by WHO-PQ, the manufacturing sites specified on the labels corresponded to those specified in the WHO list of prequalified medicines/finished pharmaceutical products. For the 23 samples listed based on a tentative approval by U.S. FDA, the information on the approved manufacturing site was specified in the list in nine cases (three products); for all nine samples it corresponded to the site stated on the labelling.

Packaging

Pack size and primary packaging for all 123 samples of prequalified products corresponded to the information specified in the WHO list of prequalified medicines/finished pharmaceutical products.

Appearance

Of 100 samples representing products prequalified by WHO-PQ, 95 conformed to the appearance approved by WHO.

Three samples of a product (all different batches) corresponded to the version of the product prior to a variation approved by WHO-PQ. The appearance of a fourth sample of the same product (another different batch) corresponded to the currently approved version. For details see Section 3.5.2.2.

Two samples of another product (both with the same batch number) were significantly different from the appearance approved by WHO. For details see Section 3.5.2.3.

Shelf life claims

The claimed shelf life of the samples was determined as the difference between manufacturing and expiry dates shown on the package labelling. For 74 of 100 samples from prequalified products , the claimed shelf life corresponded to that approved by WHO. For the remaining 26 samples the shelf life differed. These 26 samples represented nine different products for which the claimed shelf life was shorter than that approved by WHO (for 18 samples shorter by one year, for four samples by two years and for four samples by three years). There was no sample for which the claimed shelf life was longer than that approved by WHO.

These inconsistencies in claimed shelf lives can be illustrated on 12 samples (8 different batches) of lamivudine/ nevirapine/ zidovudine 30/50/60 mg dispersible tablets from one manufacturer, with a current WHO-PQR-approved shelf life of five years. Samples were collected in several countries:

[10] https://extranet.who.int/prequal/key-resources/prequalification-reports/whopars

Burkina Faso: 2 samples, all with claimed shelf life of five years

Nigeria: 3 samples, all with claimed shelf life of five years

DR Congo: 4 samples in total, including:
2 samples with claimed shelf life of five years, 1 with four years and 1 with two years.

Rwanda: 3 samples with claimed shelf life of two years (the same batch as the sample with two years shelf life collected in DR Congo).

3.5 Compliance with specifications

3.5.1 Overview of results

Testing within shelf life

The expiry dates of the samples collected in this survey ranged from December 2015 to November 2019 (sample collection took place in September – November 2015). All 126 samples were collected within their expiry date. 124 samples were tested within their shelf life. Two samples of efavirenz 600 mg tablets were sent to the laboratory before their expiry dates (4 months and 2 months, respectively), however, one sample was tested one month and the other three months after expiry date. For details of tests results see Section 3.5.2.1.

Overall rate of compliance with specifications

Of a total of 126 samples tested, 125 (99.2%) were found to be compliant. Two of 125 samples (lamivudine 150 mg tablets and lamivudine/ nevirapine/ zidovudine 30/50/60 mg dispersible tablets) did not comply with the pharmacopoeial specifications selected for this survey. However, as both these products were prequalified by WHO, they were retested by manufacturers' validated methods accepted within the prequalification procedure and found to be compliant (for details see Sections 3.5.2.3 and 3.5.2.4).

The single non-compliant sample was lamivudine 150 mg tablets, which did not comply with pharmacopoeial requirements on appearance (for details see Section 3.5.2.3).

3.5.2 Results for individual medicines

Details and tests results of the samples for each medicine tested are listed in Appendices 3-8. Within each appendix, the samples are sorted according to the countries in which they were collected. The results for each medicine included in the survey are presented below.

3.5.2.1 Efavirenz tablets (Appendix 3)

Thirty-three samples (24 batches) of efavirenz 600 mg tablets produced by six manufacturers were tested for appearance, identity, assay, weight variation, and dissolution according to the USP monograph.

All 33 samples complied fully with the specifications. The content of efavirenz ranged from 92.2% to 104.1%. In dissolution test all samples complied in stage 1, the mean amount of dissolved efavirenz ranged from 87.3% to 111.1%.

Two of the 33 samples were tested after the expiry date (one and three months after expiry respectively). However, this did not have any impact on their compliance with the specifications (assay 96.7% and 94.9% respectively, and mean dissolved amount 93.3% and 87.3%, respectively).

3.5.2.2 Efavirenz emtricitabine/tenofovir disoproxil fumarate tablets (Appendix 4)

Ten samples (10 batches) of efavirenz/ emtricitabine/ tenofovir disoproxil fumarate 600/200/300 mg tablets produced by three manufacturers were tested for appearance, identity, assay, tenofovir monosoproxil-impurity, water content, weight variation, and dissolution according to the Ph. Int. monograph.

All 10 samples complied fully with the specifications. The content of efavirenz ranged from 96.1% to 101.0%, emtricitabine from 95.6% to 102.4%, and tenofovir disoproxil fumarate from 93.2% to 100.9%. As regards dissolution, seven samples complied in stage 1 and three samples at stage 2, the mean amount of dissolved efavirenz ranged from 86.2% to 98.7%, that of emtricitabine from 90.6% to 101.2%, and that of tenofovir disoproxil fumarate from 85.8% to 98.4%.

There were samples of one product from one manufacturer which differed from specifications in their appearance. Three samples (all from different batches) had dusky pink, oblong, film-coated tablets plain on both sides. One sample from another batch had dusky pink, oblong, film-coated tablets with "V" debossed on one side and plain on the other. It was found that tablets without debossing were approved initially in the prequalification procedure. In May 2014 a variation was accepted by WHO-PQ and the appearance changed to "'V' debossed on one side". Three batches with the pre-change appearance were produced in October 2013, March 2014 and July 2014, and one sample with the current appearance was produced in July 2014. This timing corresponds in principle to the usual timing for implementation of this type of change.

During testing of efavirenz/emtricitabine/tenofovir disoproxil fumarate tablets according to the Ph. Int. monograph the laboratory faced two issues.

1. To determine dissolved APIs content in the dissolution test the "Assay" procedure should be followed, which requires keeping the solutions at about 6°C or using an injector with cooling. However, the sample and reference solutions showed strong precipitation in the HPLC autosampler when it was cooled to 6°C, because sodium dodecyl sulfate was not soluble at this temperature and concentration. Therefore the samples were only cooled to 20°C.

2. Relatively high standard deviations of assay results were observed for some samples. The large film-coated tablets (around 1.6 g) were difficult to homogenize sufficiently during the grinding step. Only a small quantity of 53 mg (corresponding to 10 mg tenofovir disoproxil fumarate) of the total of 20 grinded tablets (32 g) is prescribed to be used to prepare the sample solution. Such a small tested quantity of poorly homogenized tablets likely contributed to higher variability of results. Using a larger sample amount and inserting a dilution step was recommended to obtain better precision. These observations were provided to the secretariat of *The International Pharmacopoeia*.

3.5.2.3 Lamivudine tablets (Appendix 5)

Eleven samples (8 batches) of lamivudine 150 mg tablets produced by five manufacturers were tested for appearance, identity, assay, weight variation, and dissolution according to the BP monograph.

Nine samples complied fully with the specifications set for the survey. The assay for one sample did not comply when tested according to the BP monograph, the result was 93.3% (specification limits 95.0%–105.0%). The sample was retested using the validated method accepted within the prequalification procedure. The result of 96.1% was within the specifications, and the sample was therefore finally evaluated as compliant.

One sample did not comply with pharmacopoeial requirements on appearance. Two containers were collected for this sample, and the tablets in one container were contaminated with black drying agent from a burst sachet. Only non-stained tablets from the second container were used for testing, and all the test results were compliant. However, due to the presence of stained tablets this sample was evaluated as non-compliant. One sample of another batch produced by the same manufacturer was collected and was fully compliant, including appearance.

The content of lamivudine in all collected samples ranged from 96.1% to 98.3%. As regards dissolution, all samples complied in stage 1. The mean amount of dissolved lamivudine ranged from 97.9% to 101.6%.

The appearance of two samples of lamivudine 150 mg tablets from one manufacturer (same batch number) was significantly different from the appearance accepted within prequalification. Samples were white film-coated oval tablets, debossed '3' and '0' on either side of the score line on one side and 'H' on the other side. The appearance approved by WHO and published in WHO Public Assessment Report HA153 of May 2009 was as follows: brown, oblong, smooth film-coated tablets, scored and embossed with 'HV' on one side and '150' on the other side. It was found that no variation regarding appearance of the product had been submitted to WHO-PQ.

3.5.2.4 Lamivudine/nevirapine/zidovudine tablets (dispersible /conventional) (Appendix 6)

Sixteen samples (11 batches) of lamivudine/ nevirapine/ zidovudine 30/50/60 mg dispersible tablets produced by three manufacturers were tested for appearance, identity, assay, related substances, weight variation, dissolution of nevirapine, disintegration and fineness of dispersion. As there was no pharmacopoeial monograph for lamivudine/nevirapine/zidovudine dispersible tablets available, testing was performed according to the Ph. Int. monograph for conventional tablets. The dissolution test according to the pending USP monograph for lamivudine, zidovudine and nevirapine tablets (draft 2—for public comment) was added.

Fifteen samples complied fully with the specifications set for the survey. For one sample of lamivudine/ nevirapine/ zidovudine 30/50/60 mg dispersible tablets the result of the test for related substances did not comply when tested according to the Ph. Int. monograph, a peak of 0.6% eluting after nevirapine was found (limit not more than 0.2%). The sample was retested using the validated method accepted within the prequalification procedure. No such peak was detected and this sample was finally evaluated as compliant.

The content of lamivudine in 16 collected samples of lamivudine/ nevirapine/ zidovudine 30/50/60 mg dispersible tablets ranged from 96.5% to 103.2%, nevirapine ranged from 96.3% to 100.4%, and zidovudine from 97.8% to 102.9%. As regards dissolution, all samples complied in stage 1, the mean amount of dissolved nevirapine ranged from 93.5% to 101.5%.

One sample of lamivudine/ nevirapine/ zidovudine conventional tablets of a higher strength (150/200/300 mg) was tested in the same way as the above-mentioned samples of dispersible tablets, except for disintegration and fineness of dispersion. This sample complied fully with the specifications. The content of lamivudine was 101.6%, that of nevirapine 96.8%, and that of zidovudine 97.8%. In the dissolution test the sample complied in stage 1 with a mean amount of dissolved nevirapine of 100.5%.

3.5.2.5 Lamivudine/zidovudine tablets (dispersible /conventional) (Appendix 7)

Fifteen samples (9 batches) of lamivudine/ zidovudine 30/60 mg dispersible tablets produced by two manufacturers were tested for appearance, identity, assay, weight variation, dissolution, disintegration and fineness of dispersion. As there was no pharmacopoeial monograph for lamivudine/ zidovudine dispersible tablets available, testing was performed according to the BP monograph for conventional tablets. All 15 samples complied fully with specifications. The content of lamivudine ranged from 95.1% to 97.5%, and zidovudine from 98.8% to 102.8%. In dissolution test all samples complied in stage 1, the mean amount of dissolved lamivudine ranged from 97.2% to 101.1%, and that of zidovudine from 98.7% to 103.0%.

Six samples of lamivudine/ zidovudine 30/60 mg conventional tablets (5 batches) produced by one manufacturer were tested for appearance, identity, assay, weight variation, and dissolution according to the BP monograph for zidovudine and lamivudine tablets. All six samples complied fully with specifications. The content of lamivudine ranged from 95.6% to 99.0%, and zidovudine from 100.5% to 104.3%. In the dissolution test all samples complied in stage 1, the mean amount of dissolved lamivudine ranged from 95.2% to 100.1%, and that of zidovudine from 100.5% to 103.6%.

Thirty-one samples (28 batches) of lamivudine/ zidovudine 150/300 mg conventional tablets produced by seven manufacturers were tested in the same way as the samples of 30/60 mg conventional tablets. The content of lamivudine ranged from 95.4% to 100.7%, and that of zidovudine from 97.7% to 104.9%. In dissolution test all samples complied in stage 1, the mean amount of dissolved lamivudine ranged from 89.2% to 101.4%, and that of zidovudine from 88.3% to 102.9%.

3.5.2.6 Nevirapine dispersible tablets (Appendix 8)

Three samples (2 batches) of nevirapine 50 mg dispersible tablets produced by one manufacturer were tested for appearance, identity, assay, weight variation, dissolution, disintegration and fineness of dispersion. As there was no pharmacopoeial monograph for nevirapine dispersible tablets available, testing was performed according to the USP monograph for nevirapine tablets.

All three samples complied fully with the specifications set for the survey. The content of nevirapine ranged from 96.1% to 100.0%. As regards dissolution, all samples complied in stage 1, the mean amount of dissolved nevirapine ranged from 101.5% to 101.8%.

4 Discussion

4.1 Protocol deviations

Several instances of non-compliance with the study protocol were recorded at the sampling, sample submission and testing stages of the survey.

During sampling, 12 samples of efavirenz 600 mg tablets and 11 samples of lamivudine/ zidovudine 150/300 mg tablets respectively were collected in Zambia. Instead of only five samples of each, all collected samples were submitted for analyses to the laboratory. Similarly, in Rwanda seven samples of efavirenz 600 mg tablets and six samples of lamivudine/ zidovudine 30/60 mg were collected and submitted to the laboratory. This was however not considered a problem as altogether for the survey the expected total number of samples was not exceeded.

The protocol instructed sample collectors to focus on lamivudine/ zidovudine 30/60 mg dispersible tablets. However, in Nigeria the dispersible formulation was not available and samples of conventional tablets only were collected. In Burkina Faso, apart from four samples of the dispersible formulation one sample of conventional tablets was collected to come up with the requirement of five samples.

At the testing stage one of the contracted laboratories conducted testing on two samples after their expiry date (one month and three months, respectively), even though the samples had been received in date. This did however not affect their compliance with the specifications.

The test for uniformity of dosage units was not always performed for all samples according to the requested USP monograph <905> Uniformity of dosage units - Weight variation (corresponding to Ph.Eur. 2.4.90 Uniformity of dosage units – Mass variation) as stated in the protocol. One laboratory additionally performed the test according to Ph. Int. – Methods of analysis - 5.2 Uniformity of mass for single-dose preparations (corresponding to Ph. Eur. 2.4.5 Uniformity of mass of single-dose preparations), whereas another performed the test only according to Ph. Int. The deviations were not considered critical.

For lamivudine/nevirapine/zidovudine dispersible and conventional tablets the protocol had envisaged the dissolution test to be performed for nevirapine only according to the USP monograph for nevirapine tablets. Since there was a USP pending monograph for lamivudine, zidovudine and nevirapine tablets (draft 2—for public comment)[4] the contracted laboratory was permitted to use the USP method, and specifications from the monograph for monocomponent product were used.

4.2 Testing methods and data quality

Standardized laboratory testing methods and specifications according to established pharmacopoeias (BP, Ph. Int. and USP) were used in this survey. For products in the form of dispersible tablets (lamivudine/ nevirapine/ zidovudine, lamivudine/ zidovudine, and nevirapine) pharmacopoeial monographs were not available and the relevant monographs for conventional tablets were used.

Testing according to official pharmacopoeias made it possible to compare products from different manufacturers using one monograph. It should be kept in mind that individual products may be registered in countries or prequalified by WHO with methods and specifications which differ from those set for this survey. For this reason, as well as due to the fact that for some samples monographs for a slightly different dosage form were used, the protocol required that all prequalified products found to be out of specifications using pharmacopoeial methods should be retested using the manufacturer's validated method accepted by WHO-PQ. The decision on compliance was then based on the result of the method accepted by WHO-PQ.

The reliability of results was assured by testing at WHO-prequalified quality control laboratories.

Samples were collected, stored and transported in compliance with the survey protocol, which prevented quality deterioration during sampling and transportation before laboratory testing.

For all samples sufficient amounts of units were collected allowing proper performance of the required tests. No sample was collected after its expiry date. As mentioned under 4.1 above, two of 126 collected samples were tested after their expiry date; however, both complied with specifications.

4.3 Limitations of methodology

Due to time and resource constraints, the number of samples collected and the regions covered by the survey were rather limited. The regions were selected with a focus on the likely presence of poor quality products as well as conditions possibly affecting the product (*e.g.* climate, storage etc.). Nevertheless, in the selected regions all approved procurement and treatment sites where the target medicines could be collected were listed, and the sampling sites were selected randomly according to the instructions in the survey protocol.

No samples were collected in the informal non-regulated market. As in the selected countries the vast majority of antiretrovirals are provided to patients in treatment programmes free of charge, the informal market of antiretrovirals is expected to be negligible or non-existent.

It cannot be claimed that the samples collected and tested were fully representative of the selected medicines throughout the distribution chain in the participating countries at the time of the survey. Nevertheless, considering the above explanation, the findings provided an understanding of the quality of the target medicines at the approved procurement and treatment sites.

Since the sampling design was not entirely consistent with the previous ARV study, the possibility of comparing the outcomes is limited.

4.4 Selection of participating countries and target medicines

The previous survey focusing on antiretrovirals was organized by WHO-PQ in 2007 in Cameroon, the Democratic Republic of the Congo, Kenya, Nigeria, United Republic of Tanzania, Uganda and Zambia. Organization of a follow-up study in further countries was considered at that time. The selection of countries for this survey included countries having participated in the previous study, as well as countries participating in other WHO-PQ-supported projects and countries supplied with most of the targeted medicines by donors.

Since the conduct of the 2007 survey, HIV/AIDS treatment guidelines and availability of medicines have changed. A new risk-based approach was therefore used to select target medicines for this study, considering the probability of quality problems occurring, population exposure and the seriousness of potential quality-related harm. Medicines supplied in large volumes by a major donor partner – the Global Fund to Fight AIDS, Tuberculosis and Malaria –were expected to be in short supply locally, and were prioritized on the assumption that gaps in local supply may fuel availability of substandard and falsified products. There was also a reasonable chance to find prequalified products among Global Fund-financed medicines. Preferentially paediatric formulations and medicines for which counterfeits were reported to WHO via the WHO Rapid Alert System[11] were selected.

[11] http://www.who.int/medicines/regulation/ssffc/medical-products/en/; accessed 13 May 2017

4.5 Availability of target medicines for sample collection in surveyed countries

The sample collectors were asked to focus on medicines and dosage forms specified in the protocol only, and to collect five samples for each medicine, if possible from different manufacturers, excluding innovator products.

The relevance of each medicine for treatment of HIV-infected patients was confirmed by its listing in WHO Model List of Essential Medicines [7], and by the invitation for WHO prequalification both current at the time of selecting the medicines. In spite of this, not all selected medicines were available for sampling in all countries.

In DR Congo and Burkina Faso all except one of the selected medicines were collected. Efavirenz/ emtricitabine/ tenofovir disoproxil fumarate 600/200/300 mg tablets were absent in DR Congo and nevirapine 50 mg dispersible tablets in Burkina Faso. In Zambia two of the selected medicines were not collected, *i.e.* lamivudine/ nevirapine/ zidovudine 30/50/60 mg dispersible tablets and nevirapine 50 mg dispersible tablets. Three of the selected medicines were absent in Rwanda and Nigeria: efavirenz/ emtricitabine/ tenofovir disoproxil fumarate 600/200/300 mg tablets, lamivudine monocomponent tablets and nevirapine 50 mg dispersible tablets.

The availability of the target medicines in the survey can be summarized as follows.

- Two medicines (*efavirenz 600 mg tablet* and *lamivudine/zidovudine 150/300 mg tablets*) were sampled in all countries and were available from three and more manufacturers. The exception was Rwanda, where these two medicines were available from two manufacturers only. *Lamivudine/ zidovudine 30/60 mg dispersible tablets* were collected in all countries except Nigeria, where the same strength was collected in the form of conventional tablets (which is in line with the WHO Model List of Essential Medicines). This strength was available in all countries from two manufacturers only. It can be concluded that there is no shortage of supply of these three medicines in participating countries, at least at the procurement and treatment centres where samples were collected.
- *Lamivudine/ nevirapine/ zidovudine 30/50/60 mg dispersible tablets* were collected in all participating countries except Zambia. According to the information received from the collectors, in Zambia this medicine has been included in treatment guidelines but paediatric dosage forms were often out of stock or there were not enough packages to collect samples and still keep the product available for patients. In countries where samples of this medicine were collected, products from only one or two manufacturers were typically available.
- *Lamivudine tablets* were collected in Burkina Faso, DR Congo and Zambia. Only samples of the 150 mg strength were collected although the 300 mg strength was also eligible for collection within this survey. This is consistent with the WHO Model List of Essential Medicines that includes only the strength of 150 mg. In Nigeria and Rwanda only fixed-dose combinations with lamivudine are used according to treatment guidelines, therefore no samples of monocomponent lamivudine were collected.
- The lowest availability was observed for *efavirenz/emtricitabine/tenofovir disoproxil fumarate 600/200/300 mg tablets* (collected in Burkina Faso and Zambia only) and *nevirapine 50 mg dispersible tablets* (collected in DR Congo only). Efavirenz/ emtricitabine/ tenofovir disoproxil fumarate 600/200/300 mg tablets were not included in treatment guidelines in DR Congo, Rwanda and Nigeria, since combinations with lamivudine are used instead. Nevirapine 50 mg dispersible tablets were not included in the essential medicines lists of Burkina Faso and Rwanda, where only fixed-dose combinations with nevirapine are used. In Nigeria

monocomponent nevirapine was used in the form of oral suspension but not as dispersible tablets. In Zambia, nevirapine dispersible tablets were used for treatment, but at the sites visited they were either out of stock or there were not enough packages to collect samples and keep the product available for patients.

Usually the availability of a product from several manufacturers may indicate lesser vulnerability to shortages of a given product in a country. Therefore, attention was paid in this survey to the number of manufacturers whose products were collected. Products from several manufacturers were found in countries for monocomponent efavirenz and fixed-dose combination lamivudine/ zidovudine. However, this may be largely because the medicines used in treatment programmes were prequalified products purchased through international procurement.

Each of the selected medicines was available at least in one country. Absence of some medicines in certain countries reflects therapeutic practice in a given country, such as the use of combination efavirenz/ lamivudine/ tenofovir disoproxil fumarate instead of efavirenz/ emtricitabine/ tenofovir disoproxil fumarate, or the use of lamivudine in fixed-dose combinations, not a monocomponent formulation. Procurement policies and distribution issues may also play a role in limiting the availability of certain medicines, for example paediatric dosage forms such as nevirapine dispersible tablets, which were often out of stock or available in small amounts only.

4.6 Manufacturers and WHO prequalification

In total, 29 different products produced by eight Indian manufacturers were sampled in this survey. Twenty-eight of the 29 products were included in the WHO list of prequalified medicines/finished pharmaceutical products at the time of the survey. This included 22 products that were prequalified on the basis of evaluation carried out by WHO-PQ, and six products listed based on U.S. FDA tentative approval (Table 7). Only one of the products collected was not prequalified.

Table 7: Numbers of products on the WHO prequalification list and numbers collected in the survey, for each target medicine

Target medicine	Medicine code	Number of products on the WHO prequalification list			Number of products collected in the survey		
		Total	Assessed by WHO	Approved by U.S. FDA	Total	Assessed by WHO	Approved by U.S. FDA
Efavirenz 600 mg tablets	EFV	**10**	8	2	**5**	4	1
Efavirenz/emtricitabine/ tenofovir disoproxil fumarate 600/200/300 mg tablets	TEE	**8**	6	2	**3**	3	0
Lamivudine 150 mg tablets	LAT	**10**	8	2	**5**	4	1
Lamivudine/nevirapine/ zidovudine 30/50/60 mg dispersible tablets	LNZ	**3**	2	1	**3**	2	1
Lamivudine/zidovudine tablets	LZT						
30/60 mg dispersible tablets		**2**	1	1	**2**	1	1
30/60 mg conventional tablets		**3**	2	1	**1**	1	0
150/300 mg tablets		**14**	10	4	**7**	6	1
Nevirapine 50 mg dispersible tablets	NEV	**3**	2	1	**1**	0	1
Total		**53**	39	14	**27***	21	6

* In addition, one sample of LNZ 150/200/300 mg (not targeted in the survey) and one sample of a non-prequalified EFZ 600 mg tablet product were collected in the survey, *i.e.* a total of 29 products.

The table shows that in this survey samples were taken of about half of the products on the WHO prequalification list that corresponded to the selected target medicines An interesting case is lamivudine/ nevirapine/ zidovudine 30/50/60 mg dispersible tablets, for which samples of all three products on the WHO list were collected in the survey.

Of the total of 29 products collected in the survey, 28 were on the WHO prequalification list. The high prevalence of such products in distribution can be a result of several contributing factors:

- Quality assurance policies of procuring organizations, which rely on the WHO list or conditions for financial support to countries to purchase products of assured quality,
- Competitive advantage of quality-assured products as regards overall costs, availability and other conditions,
- Interest of manufacturers to economize investment in prequalification by active marketing/exporting policy.

Companies choose different pathways to have their products included in the WHO list of prequalified finished pharmaceutical products. The 28 listed products sampled in this survey came from a total of 8 different manufacturers. One company had four U.S. FDA-approved products included in the survey and was using this pathway exclusively. Another had two U.S. FDA-assessed products and four WHO-PQ-assessed products, including two that were also US-FDA-approved. All 18 products from the remaining six companies were evaluated by WHO-PQ, 13 of them were also U.S. FDA-approved (see Table 4 on page 26 and Appendix 2 for details). The reasons and/or advantages of using each pathway were not explored.

Local manufacture

No samples of locally manufactured products were collected in any of the participating countries. Among the five survey countries, only Nigeria has domestic manufacture of antiretroviral medicines, and according to information from the collectors some locally manufactured products are supplied to private centres. However, HIV/AIDS treatment in the countries of collection is predominantly organized through treatment programmes, which administer substantially higher volumes of medicines than is the case in private practice. This confirmed the established notion that antiretrovirals are generally procured by international procurers in line with policies of donors, and purchases of prequalified products are prioritized. Incentives for local production may be limited and not sufficiently attractive for local manufacturers.

Redistribution

It was relatively common that samples were collected in other countries than those indicated by the manufacturers as destination for the supply (approx. 40% of samples). Assuming that the information from the manufacturers was correct, this demonstrates frequent re-distribution of medicines among countries and illustrates the complexity of supply channels, involving intermediate parties – including international procuring companies – and treatment programmes. This makes it difficult or even impossible for manufacturers to control their products in the countries of use. Regulatory authorities should focus on the risks presented by such complex supply channels. Although such situations can increase the likelihood of occurrence of poor quality medicines, this has not been observed in the current survey.

Conformity with conditions approved by WHO-PQ

It was not specifically verified with manufacturers whether each product was supplied "as prequalified" in full compliance with all WHO currently approved conditions or if there were some deviations *e.g.* in specifications of finished formulations or APIs. However, a verification of conformity with conditions approved by WHO-PQ, using the public information specified in the list and WHO Public Assessment Report, showed that the manufacturing sites specified on the labels, pack sizes and primary packaging corresponded to those specified in the list. With respect to the appearance of samples, two samples of lamivudine tablets were significantly different from the appearance accepted within prequalification and no variation regarding appearance of the product has been submitted to WHO-PQ (see Section 3.5.2.3). This deviation will be further investigated by WHO inspectors after confirmation from the country of collection that this product was purchased "as prequalified".

The comparison of shelf lives of collected samples with those approved by WHO showed differences in 26% of samples. This did not represent a risk of quality deterioration as in all cases the shelf lives of the collected samples were shorter by one to three years than those approved by WHO-PQ. It can have, however, implications for procurement, distribution and availability of products.

It should be kept in mind that during prequalification of a product WHO-PQ assesses stability studies against requirements for zone IVb , *i.e.* manufacturers have to submit accelerated stability studies performed at 40°C, and 75% relative humidity for six months as well as a minimum of 12 months data for storage under zone IVb long term conditions (30°C and 75% RH) for consideration of a shelf life of usually 24 months. For a shelf life longer than 24 months, real time stability study must be submitted up to the proposed shelf life. Often a shelf life of two years is initially accepted in the prequalification procedure, and manufacturers then gather additional data to apply for an extension. This situation is reflected in Appendix 2, which lists both the shelf life of each product as accepted during the initial PQ procedure and as approved at the time of writing the report.

The reasons of the shorter shelf lives claimed for the samples collected in countries might be either an extension of a shelf life by WHO-PQ after the production date of the sample, or shorter shelf lives accepted by procurers or approved during national approval processes in countries.

4.7 Registration status of sampled products

Among other things, the collectors evaluated the registration status of the samples, *i.e.* whether the sampled products were authorized by the competent NMRA for marketing and distribution in the country of collection. If a sample of an unregistered product was collected, the collectors documented the basis on which the product was supplied and placed on the market.

All products were placed on the market legally. They were either registered, or supplied through various specific mechanisms to enable the supply of needed medicines.

The survey also revealed marked differences in the approach to registration of sampled products in individual countries:

- In Nigeria and Zambia rigorous registration policies were applied and all collected products were registered or their registration was pending.
- In Burkina Faso, there was an effort to register the sampled products, but more than half of products were not registered and were supplied as a donation or on the basis of special permission. There is a regulatory requirement that any unregistered product purchased by the central medical store should be registered within the following six months, but the compliance with this requirement is generally poor.

- In DR Congo and Rwanda none of the sampled products was registered and specific regulatory mechanisms (special permission or central supply to government centres, respectively) were applied to make the unregistered products available. Both countries are trying to gain control over unregistered products. In DR Congo all supplied antiretrovirals have since been registered after an accelerated procedure in 2016 and in Rwanda registration of antiretrovirals is underway.

As almost all tested medicines could be found in the WHO list of prequalified medicines/finished pharmaceutical products, the rather relaxed attitude to rigorous registration in several countries can be explained by their reliance on existing regulatory capacity elsewhere and application of simplified quality assuring processes. It has not been followed to which extent countries verified whether selected antiretrovirals were approved and imported fully in line with prequalified conditions, *e.g.* by the WHO collaborative registration process [8]. Four of the countries (Burkina Faso, DR Congo, Nigeria and Zambia) were participating in the WHO collaborative registration process. However, at the time of sample collection only Nigeria had registered two products following reliance of the WHO collaborative procedure for lamivudine 150 mg and lamivudine/zidovudine 150/300 mg tablets.

4.8 Storage conditions in sites of sample collection

Information on storage conditions was obtained for all samples. According to the reports obtained from collectors, storage conditions were properly controlled at the procurement/ treatment centres visited for 90% of collected samples; temperature and relative humidity were recorded and found to be within acceptable limits. 5% of collected samples were kept in rooms without controlled conditions, but equipped with air-conditioning which in principle assured acceptable storage conditions.

For the remaining 5% of samples the collectors reported uncontrolled storage conditions, with temperatures above 30°C or without information on temperature. Despite these observations, none of the samples concerned showed substandard quality.

With regard to the situation in countries, storage conditions were controlled at all sampling sites in DR Congo, Nigeria and Rwanda. In Zambia storage conditions were not controlled in 1 of 14 visited sites (a private hospital, where the recorded temperature was slightly above 30°C). In Burkina Faso storage conditions were controlled at 3 of 11 visited sites. At three sites conditions were not controlled but rooms were air-conditioned, and at five sites (hospitals and treatment centres both public and private) conditions were not controlled with temperatures above 30°C or unrecorded temperatures.

It can be concluded that storage conditions at the centres visited were well under control in four countries. In Burkina Faso not all sites demonstrated rigorous control over storage of collected medicines, but no failure of tested quality parameters was observed. Interpretations of this situation can be manifold (short storage period, no real temperature extremes, relatively stable products etc.). Nevertheless, resources are lacking for proper storage of medicines in hospitals and treatment centres. The sample collectors informed the Ministry of Health of Burkina Faso and tried to organize some support through donors to improve the situation.

4.9 Quality findings

Overall compliance

In this study 125 of 126 samples (99.2%) were found to be compliant with the specifications set for the survey. None of the 126 collected samples failed to comply with the specifications for any of the conducted laboratory tests. The only non-compliant sample - lamivudine 150 mg tablets - did not comply with pharmacopoeial requirements on appearance. Tablets in one of two collected containers from the same batch were stained with black drying agent from a burst sachet. Although this sample did not fail any analytical tests (only non-stained tablets from the second container were used for testing) it was evaluated as non-compliant because of the appearance problem. The matter indicates a problem in GMP compliance and will be investigated during the next WHO inspection.

Retesting

Two samples (lamivudine 150 mg tablets and lamivudine/ nevirapine/ zidovudine 30/50/60 mg dispersible tablets) did not comply with the pharmacopoeial specifications selected for this survey in initial testing. In line with the protocol, these samples were retested by validated methods accepted within the prequalification procedure and were found compliant.

1. For one sample of lamivudine 150 mg tablets – the only sample from that manufacturer collected in the survey – the lamivudine content was found slightly below the limit when tested according to the BP monograph. The sample was retested using the validated manufacturer's method accepted within the prequalification procedure. This method differed slightly from the BP method in sample preparation procedures as well as in HPLC conditions. The result of retesting was within the specification requirements, although close to the lower acceptance limit. The sample was evaluated as compliant.
2. One sample of lamivudine/ nevirapine/ zidovudine 30/50/60 mg dispersible tablets (one of 12 samples of 8 different batches collected from that manufacturer), did not comply in the test for related substances when tested according to the Ph. Int. monograph method for lamivudine/ nevirapine/ zidovudine conventional tablets. One peak eluting after nevirapine was found to be above the limit. When retested by the validated method accepted within the prequalification procedure which differed in HPLC conditions no such peak was detected and this sample was evaluated as compliant. All 11 samples of different batches from the same manufacturer, as well as four samples from two other manufacturers complied in the related substances test according to the above mentioned Ph. Int. monograph.

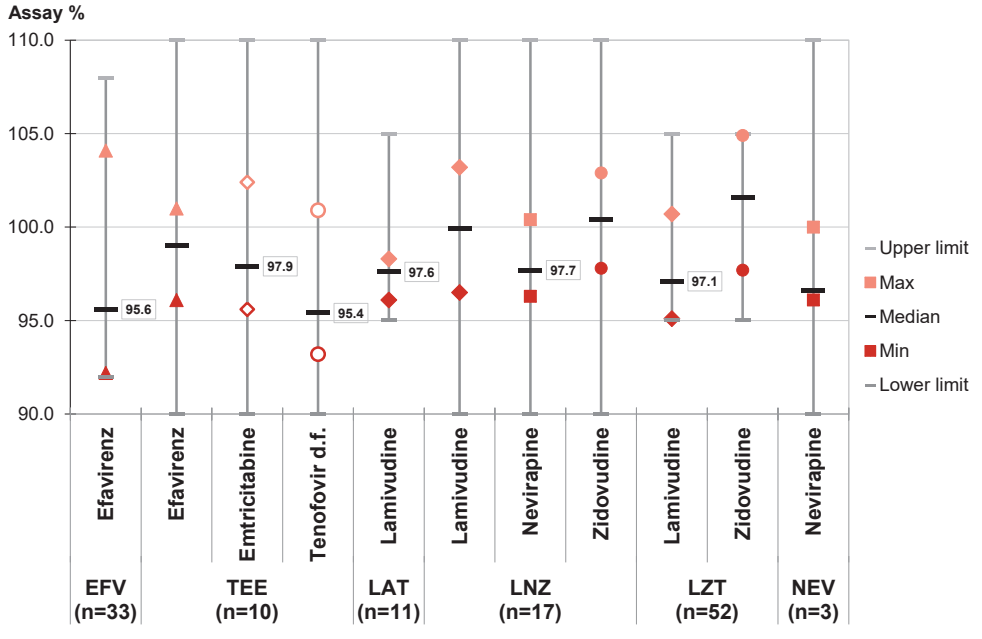
Expiry dates

Two samples of efavirenz 600 mg tablets produced by two different manufacturers were tested after the expiry date. The shelf life of both products was three years and the samples were tested one and three months after expiry respectively. Both samples complied with specifications.

Assay

The assay results for each API are summarized in Figure 1. The Figure shows that even though all the results complied with specifications, the majority of results were below 100% of labelled content, and some were close to the lower acceptance limit. Median content values below 98% are labelled in the graph and are discussed further on page 43.

Figure 1: Assay results for tested samples*



* Dosage forms and strengths not differentiated.

There was a notable product-to-product variation in assay results for the 33 samples of efavirenz 600 mg tablets, which ranged from 92.2% to 104.1% of labelled content. The median was 95.6%, with mean of 96.0 and a standard deviation of 2.39. All the samples met the requirements for uniformity of dosage units; no tablet mass deviated by more than ±5% from the mean mass of 20 tablets. The assay results from manufacturers' certificates of analysis at release ranged from 97.5% to 102.9%. This product-to-product variation was not noted for the efavirenz/ emtricitabine/ tenofovir disoproxil fumarate 600/200/300 mg tablets.

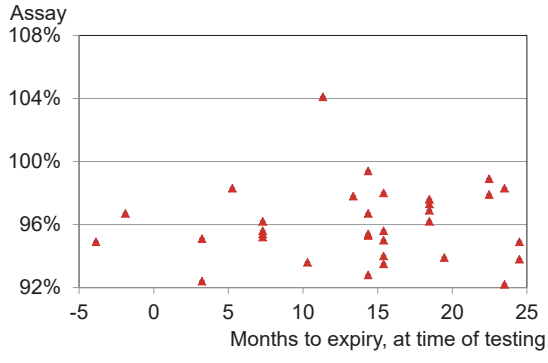
In pharmaceutical formulations it is generally established that if the API forms the greater part of the tablet mass any weight variation should be related to the content of the API. A review of the PQ-approved formulations showed that content of efavirenz ranged from 46 to 50% w/w for the efavirenz tablets and was about 38% w/w for the efavirenz/ emtricitabine/ tenofovir disoproxil fumarate 600/200/300 mg tablet formulations. The same trend should have been noted in the assay for both formulations. The weight variation and assay variation for one batch should be of the same order. This was however not the case. No further review could be conducted since the test for related substances was not included in the test protocol. This could have been relevant to establish mass balance.

Content in relation to remaining shelf life

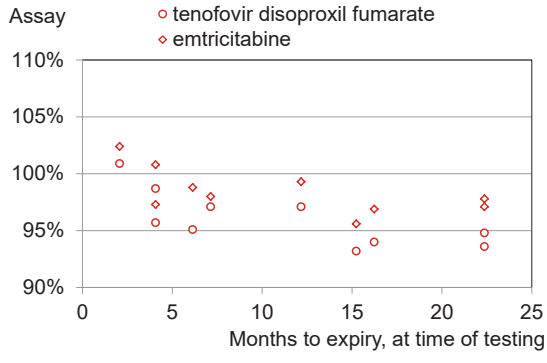
One can hypothesize that a lower content of active principles is related to product aging. To understand this phenomenon better, individual assay values were plotted against time remaining to expiration (derived from the labelled manufacturing and expiry dates). However, a graphical presentation of data for the most suspected APIs (those with median content values below 98% in Figure 1 above)[12] did not suggest that older samples contained less API than newer ones (see Figures 2–6). Interestingly, the values recorded for tenofovir disoproxil fumarate and emtricitabine were the lowest in the samples which still had 16-23 months to expiry, and highest in the samples which were close to expiration (see Figure 3).

Figures 2–6: Content of active pharmaceutical ingredient in samples, by time remaining to expiry

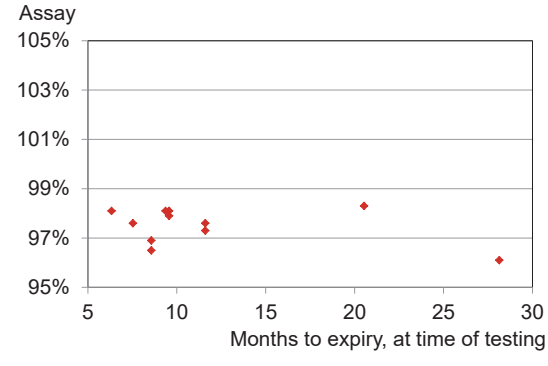
- Figure 2: Efavirenz tablets



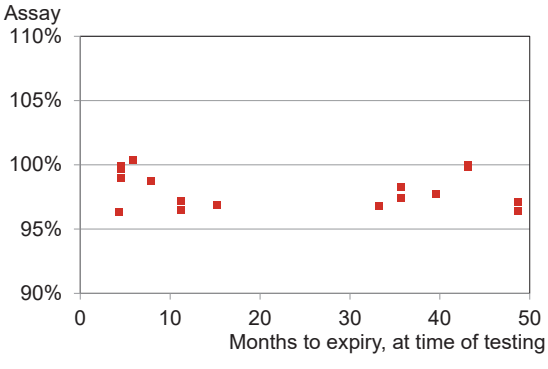
- Figure 3: Efavirenz/emtricitabine/tenofovir disoproxil fumarate tablets



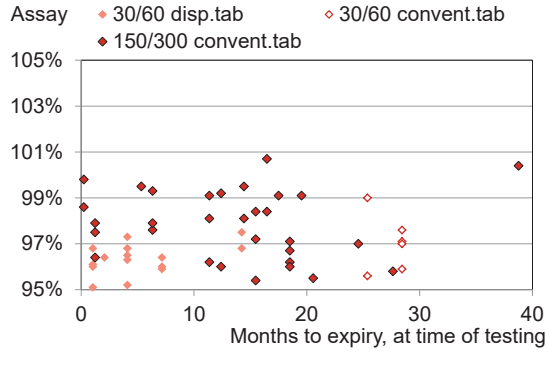
- Figure 4: Lamivudine tablets



- Figure 5: Lamivudine/nevirapine/zidovudine tablets: content of nevirapine



- Figure 6: Lamivudine/zidovudine tablets: content of lamivudine

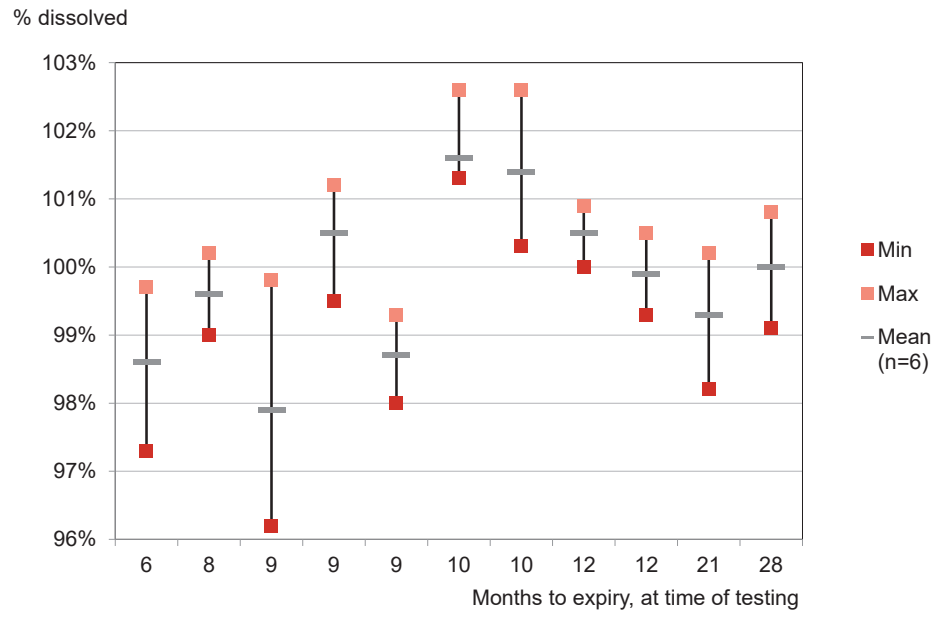


[12] Nevirapine tablets results were not considered because of the small number of samples (3 samples from 2 batches).

Dissolution

The results for all 11 tested samples of lamivudine tablets ranged from 97.9 to 101.6% at 45 minutes, all at S1 stage, meeting the PQ acceptance criteria. An overview of the results, in relation to remaining time to expiry, is provided in Figure 7.

Figure 7: Dissolution results for lamivudine tablets



On review of the four WHO-PQ-approved lamivudine 150 mg tablets products it was noted that they had approved acceptance criteria for dissolution (Table 8).

Table 8: Acceptance criteria for dissolution for lamivudine tablets as approved by WHO-PQ

Product[13]	WHO-PQ-accepted criteria
Product A	Not less than 75% (Q) in 30 minutes (not less than 80% in 30 minutes at S1 stage)
Product B	Not less than 80% (Q) in 30 minutes
Product C	Not less than 80% (Q) in 15 minutes
Product D	Not less than 80% (Q) in 30 minutes

Lamivudine API has been classified by WHO PQ[14] as BCS Class III up to a dose of 300mg, with characteristic low permeability and high solubility. It is therefore anticipated that solubility would be high (the highest dose is soluble in 250 mL or less of aqueous media over the pH range of 1.2–6.8 at 37ºC) and Lamivudine 150mg tablets would be rapidly dissolving (>85% of the labelled amount of drug substance, Q, dissolves within 30 minutes using USP apparatus I or II in a volume of 900 ml or less of buffer solutions); that is the dissolution rate would rather depend on the disintegration time of the tablets than the solubility of the API . However the BP specifications used for the study (NLT 75% (Q) in 45 minutes) may not be discriminatory. Regulators and manufacturers should take heed and apply product specific criteria that enable better discrimination; the pharmacopoeial specifications should be regarded as the minimum requirements and product specifications could be tighter if and when supported by data.

[13] Products are not identified, as specifications are not public information.

[14] "Notes on Biopharmaceutics Classification System (BCS)-based Biowaiver Applications" https://extranet.who.int/prequal/sites/default/files/documents/35%20Biowaiver%20general_Nov2014.pdf; accessed 14 March 2017)

Water content

It is established that formulations containing emtricitabine and tenofovir disoproxil fumarate are moisture-sensitive as both APIs are susceptible to aqueous hydrolysis[15] and degrade in high moisture/temperature conditions with potentially increased incompatibility between them. Water content in all tested batches was within the limits (not more than 50 mg/g), ranging from 7.7 mg/g to 10.8 mg/g, and the related substances were within the acceptance criteria.

Authenticity of products

As one of the study objectives was to explore the presence of potential counterfeited products, the manufacturers of collected products were asked for verification of authenticity of each collected batch. The responses of manufacturers confirmed authenticity of all collected samples and minimised the possibility that falsified products were collected.

4.10 Recommendations from survey wrap-up meeting

During the wrap-up meeting in March 2017 all countries commended the experiences of participating in the survey and had already starting implementing some principles of the survey into their own post-market surveillance activities. The following recommendations were made:

For WHO

It was recommended that whenever multi-country studies are conducted – especially in countries whose National Quality Control Laboratories (NQCL) are not prequalified or ISO-accredited – in-country testing should also be considered and elements of proficiency testing included. This would be useful for capacity-building and confidence-building at NQCLs.

During sample collection, non-destructive screening in-country should be performed before samples are submitted to the designated laboratories.

WHO was encouraged to establish a sharing/repository platform for NQCLs to share testing results and other relevant data, particularly at a regional level.

The use of data loggers for tracking of shipping conditions was recommended for future surveys.

Technical reports and analyses were provided in addition to the standard certificates of analyses on a unique basis for this survey. Some participating laboratories recommended that WHO should provide them with additional guidance and/or capacity-building, as a follow-up to its request for standard certificates of analysis and additional technical reports for the purposes of this survey.

To countries

National authorities should cooperate with regard to sharing of information on the quality of products circulating in countries.

Countries should focus on post-market surveillance testing rather than pre-registration testing.

To pharmacopoeias

Some specific comments on the assay and dissolution test methods in the Ph. Int. monograph for efavirenz, emtricitabine, tenofovir disoproxil fumarate tablets in relation to test sample preparation and handling of media and analytes were discussed (see page 31). These were submitted to the WHO team with oversight of the Ph. Int. for consideration.

[15] EMA. Truvada: EPAR – Scientific discussion. First published 22/11/2005. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000594/WC500043716.pdf; accessed 13 May 2017

5 Conclusions

The quality survey of selected antiretrovirals in Burkina Faso, Democratic Republic of the Congo, Nigeria, Rwanda and Zambia was conducted in compliance with the pre-established protocol. The survey was organized by WHO in close cooperation with national regulatory authorities in the five countries. Apart from providing a snapshot picture on the quality of collected samples, the survey generated information about the availability of the selected medicines, their prequalification and registration status, and storage conditions in procurement and treatment centres in participating countries. The participation of national regulators in the sampling and testing by reliable quality control laboratories according to the common protocol enabled not only a verification of medicines quality but also led to training, cooperation and gathering of stimuli for corrective and preventative actions in participating countries.

Robust data were generated on the quality of the samples of antiretrovirals collected in the survey. However, when interpreting the survey outcomes it should be kept in mind that the results relate to a limited set of countries, a specific selection of medicines and a limited number of samples.

The study verified the quality of 126 samples of selected ARVs, which was its main objective. Although medicines with higher probability of substandard quality were targeted, the collected samples proved to be uniformly of good quality. The pharmacopoeial and manufacturers' methods and specifications used in the survey did not identify any quality problems, with the exception of one issue in sample appearance. Because of absence of negative results, questions related to detailed analysis of potential quality deficiencies could not be answered. However, the study provided other findings and observations.

It was demonstrated that pharmacopoeial methods are not always appropriate for quality control of specific products. Although in the majority of cases they seemed to be sufficient to verify product quality, there were two cases when – contrary to approved manufacturers' methods – they provided marginally failing results.

Compared with the results of a study organized by WHO-PQ in 2007, an improvement of ARV quality in official distribution and treatment centres was noted, the failure rate marginally decreased from 1.8% to 0.8% of samples. The share of prequalified products among samples increased from 53% to 98%.

The survey confirmed the positive impact of WHO prequalification in making products of consistently good quality available for procurement in countries. Repeatedly documented zero failure rates of prequalified products demonstrate that WHO prequalification reliably assures uniform quality standards.

As expected, collected products were produced by foreign manufacturers all from India without representation of local production. The complexity of procurement and distribution channels of ARVs was demonstrated by the fact that some manufacturers did not know to which markets their products were finally supplied. This suggests that re-distribution of medicines among countries was frequent. Regulators should focus on conditions in such complex supply channels.

In principle, all the selected medicines were available at procurement and treatment centres. However there were differences in the numbers of generic versions of a given medicine that were available. The availability of certain target medicines was influenced by local therapeutic guidelines and practices. As per protocol the sample collectors did not collect samples of innovator products, and no information was recorded on their availability.

While rigorous registration policies are applied in several participating countries, other legally acceptable mechanisms that bypass normal registration processes are also used to supply needed medicines. To which extent these mechanisms rely on assessment and inspection performed by other parties, such as WHO and U.S. FDA, remains to be explored in more detail.

The survey indicated that storage conditions in procurement and treatment centres in participating countries were in principle under control, and that any shortcomings did not have a negative impact on medicines quality.

The method of multistate collaborative sampling and centralized testing, with common data analysis and adoption of country-specific corrective and improvement measures, has again proven to be a useful instrument in independent quality monitoring of prioritized medicines. It was recommended that WHO should make efforts to develop data-sharing platforms or repositories of testing results for countries.

The participating countries recommended that future studies should incorporate in-country screening and/or testing, for subsequent comparison with the results obtained by WHO-contracted laboratories.

6 References

1 *Global AIDS Update. UNAIDS 2016 (*http://www.who.int/entity/hiv/pub/arv/global-AIDS-update-2016_en.pdf?ua=1 ; accessed 23 November 2016).

2 *Survey of the quality of antiretroviral medicines circulating in selected African countries*. Geneva: World Health Organization;
2007 (https://extranet.who.int/prequal/sites/default/files/documents/ARV_survey_1.pdf; accessed 30 June 2017).

3 *Survey of the quality of selected antimalarial medicines circulating in six countries of sub-Saharan Africa*. Geneva: World Health Organization;
2011 (https://extranet.who.int/prequal/sites/default/files/documents/WHO_QAMSA_report_1.pdf ; accessed 30 June 2017).

4 *Survey of the quality of anti-tuberculosis medicines circulating in selected newly independent states of the former Soviet Union*. Geneva: World Health Organization;
2011 (https://extranet.who.int/prequal/sites/default/files/documents/TBQuality-Survey_Nov2011_1.pdf ; accessed 30 June 2017).

5 *Survey of the quality of medicines identified by the United Nations Commission on Life Saving Commodities for Women and Children.* Geneva: World Health Organization;
2015 (https://extranet.who.int/prequal/sites/default/files/documents/UNCoLSC_2015.pdf; accessed 30 June 2016).

6 The International Pharmacopoeia*, Sixth Edition, 2016.* Geneva: World Health Organization; 2016. (http://apps.who.int/phint/en/p/about/; accessed 30 June 2017).

7 *WHO Model List of Essential Medicines. 19th List.* April 2015 (amended November 2015). Geneva: World Health Organization; 2016 (http://www.who.int/medicines/publications/essentialmedicines/en/; accessed 14 March 2017).

8 Collaborative procedure between the World Health Organization Prequalification Team and national regulatory authorities in the assessment and accelerated national registration of WHO- prequalified pharmaceutical products and vaccines. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. *Fiftieth report*. Geneva: World Health Organization; 2016: Annex 8 (WHO Technical Report Series, No. 996;
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex08.pdf?ua=1 ; accessed 14 March 2017).

Appendices

Appendix 1 Survey protocol

Survey of the quality of selected antiretroviral medicines circulating in selected countries

1. Glossary of terms and abbreviations

Country codes (for the purposes of coding samples):

- Burkina Faso = BF
- Democratic Republic of the Congo = DRC
- Nigeria = NG
- Rwanda = RW
- Vietnam = VN
- Zambia = ZM

Medicines abbreviations (for the purposes of coding samples):

- Lamivudine tablets = LAT
- Efavirenz tablets = EFV
- Nevirapine tablets = NEV
- Lamivudine/nevirapine/zidovudine tablets = LNZ
- Efavirenz/emtricitabine/tenofovir disoproxil fumarate tablets = TEE
- Lamivudine/zidovudine tablets = LZT

Sample:	for the purposes of this project means an item collected from each medicine's presentation (identified by the name, content of APIs, dosage form, strength, batch number and manufacturer) at the same collection site. That means that a product of the same name, content of APIs, the same dosage form, strength, batch and from the same manufacturer collected in two different sites represents two samples.
Procurement centre:	for the purpose of this project means a point, where a medicine enters the country, central stores and stores, where a medicine is kept during the in country distribution.
Treatment centre:	for the purpose of this project means the final site, where a medicine is delivered and where it is provided to a patient.

API	Active pharmaceutical ingredient
ARV	Antiretroviral
BP	British Pharmacopoeia
FDC	Fixed-dose Combination
GMP	Good Manufacturing Practice
HPLC	High performance liquid chromatography
INN	International Nonproprietary Name for pharmaceutical substances
NGO	Non-governmental organization
NMRA	National medicines regulatory authority
Ph. Int.	The International Pharmacopoeia
PQT	WHO Prequalification Team
PMS	Post-market Surveillance
QCL	Quality Control Laboratory
SSFFC	Substandard/spurious/falsely labelled/falsified/counterfeit
USP	United States Pharmacopeia
WHO	World Health Organization

2. Background

A lot of effort and finance have been expended on trying to optimize the treatment of diseases and improving access, but such investment is lost if the medicines the patients take are of poor quality.

Unfortunately, according to the World Health Organization (WHO) 30% of the world´s national medicines regulatory authorities (NMRAs) do not have functional capacity and in low-income countries the NMRAs often lack sufficient financial and human resources to carry out controls in a stringent and comprehensive way. Most of these countries are therefore recipients of donor supported public financing for pharmaceutical supplies.

In the last WHO-coordinated ARV study of 2007[16] none of the antiretrovirals sampled had any critical quality deficiencies that would pose serious risk to patients. Among the 394 samples collected, the overall failure rate was 1.8%. The content of active pharmaceutical ingredient of one sample exceeded the upper limit. One of 163 samples tested for disintegration failed to disintegrate completely within 30 minutes, and two of 153 samples tested for dissolution showed lower results than required. Fifty-three percent of sampled products were WHO-prequalified. Information on registration by NMRAs was available for 285 products; of these, 84% were registered. Products not registered at the time of sampling were found in three countries, mostly at private sector facilities, and constituted 12% of the total of 394 sampled products.

Following discussions with affected countries after previous studies, several recommendations on corrective and preventative actions were made and are largely incorporated in the focus of the current study.

Besides evaluation of other new markets the current study hopes to evaluate whether for the previously included markets, any of the recommendations have been implemented and the outcomes thereof. The evaluation will however be limited since such a prospective study requires that the sampling design is consistent through time. Unlike in previous studies, this study will also include a review of some aspects of product information that accompanies supplied products or is available for the health professionals and patients.

The current (third) invitation for Expression of Interest for prequalification of quality control laboratories (QCL) aims to promote testing of pharmaceutical products internationally by quality control laboratories which meet WHO-recommended standards and to increase the range of quality control laboratories for which the acceptability for use by United Nations agencies has been proven. 38 QCLs are already prequalified and forty-two (42) QCLs are working towards WHO prequalification (PQ). There is therefore an apparently fairly good distribution of national or private/commercial prequalified QCLs providing recipient countries access to evaluation of the quality of prequalified medicines. Some of the prequalified QCLs in sub-Sahara Africa have however not been regularly used for the intended purpose and are therefore included as testing facilities in this study partly to evaluate their capacity.

This study also aims to help to improve capacity of NMRA inspectors to coordinate post-market quality surveillance.

This study is a snapshot of the medicine quality situation in the markets where samples are to be collected and therefore will have some important limitations in making conclusions. The survey will also not cover remote treatment sites or any informal sources where higher failure rates may be anticipated.

3. Objectives

The main objective of this project is to assess the quality of selected antiretrovirals obtained at authorized/accredited public and private sector distribution and treatment sites in selected countries using laboratory tests against quality criteria and review of product information.

The project also aims to determine the following:

- What proportion of ARV medicines samples, including fixed-dose combination products and paediatric formulations, collected at approved procurement and treatment centres fails quality testing?
- Which specific quality tests do samples fail, if any?
- Are any of the deficiencies critical, *i.e.* could they affect treatment efficiency and/or cause harm to the patient?
- For those countries included in the 2007 study, are there any noticeable changes in medicine quality?

[16] http://www.who.int/prequal/info_general/documents/ARV_survey.pdf

In addition the project will gather information on the following:

- What are the supply chains through which poor quality medicines are likely distributed and the market segments they serve? We will however only evaluate at 2 levels of distribution hence exclude the informal sector.
- How does the proportion of poor quality medicines vary at different levels of the regulated distribution chains?
- How does the proportion of poor quality medicines vary by medicines produced within country versus those imported from different countries?
- How does the proportion of poor quality medicines vary whether they are registered or not?
- In a limited way, whether prequalified laboratories in the proximity (and therefore potentially accessible) to the surveyed markets have capacity to provide acceptable quality of testing service.
- What proportion of prequalified products is available at the various distribution levels?
- How useful is the information that is available on the prequalification website on prequalified products?
- Information that is supplied with the sampled products.

The results of this survey are expected to also assist responsible authorities in the surveyed countries to evaluate their markets and propose possible strategies and implementation plans to address any problems identified.

Although product information will be collected and collated with the samples in the study, this will be reviewed for compliance with local registration, prequalification (where applicable) and WHO requirements in a separate study. This separate study will evaluate the quality of product information that is available for the health professionals distributing or dispensing the products. Similarly, for the evaluation of prequalified laboratories.

Limitations of the survey

Due to time and resource constraints, this survey cannot fully evaluate quality of target medicines throughout the distribution chain to assess the effect of storage and transportation conditions and/or evaluate the risk of patients' exposure to substandard medicines.

The survey findings will be relevant only to tested samples and extrapolation to other produced batches (or even within a tested batch) will be limited as this would require evaluation of manufacturers' GMP compliance and assessment of products' dossiers.

The tests conducted cannot completely identify problems of bioavailability, if they exist.

Since the sampling design may not be consistent for those countries that have been surveyed before, the comparison of outcomes and effectiveness of corrective actions since the previous study will be limited.

4. Methodology

4.1 Selection of medicines and countries for sampling and testing

Medicines that were supplied in 2013-2014 to recipient countries by a major donor partner, the Global Fund to Fight AIDS, Tuberculosis and Malaria, were the main target as they are expected to represent gaps in local supply as well availability of prequalified products (See Annex 1A). Gaps in local supply are generally expected to fuel availability of substandard, spurious, falsified, fake and/or counterfeits. To optimize use of resources available for this survey a benefit-risk analysis was performed on the most commonly supplied products in terms of volume/numbers to various countries and regions (See Annex 1B).

In the past 5 years there has been a steady increase in prequalification of paediatric formulations and these were not been targeted in previous studies and are therefore deliberately included.

In order to acquire a wider picture of the quality of medicines available on the market, as many samples as possible that are produced by different manufacturers will be collected and tested.

Information from the WHO team responsible for monitoring Substandard/Spurious/Falsely-labelled/falsified/counterfeit (SSFC) medical products was also used in priority setting. Current records show that about fifty (50) prequalified products have been counterfeited to date. These include emtricitabine/ tenofovir disoproxil fumarate tablets, lopinavir/ritonavir tablets and lamivudine/nevirapine/zidovudine tablets. However, not all could be included in the list due to funding limitations, availability of reliable verified test methods or the products had already been included in other recently published studies. Verifications will be made with manufacturers to confirm source of products.

The following risked based criteria were therefore considered (see Annexes 1A and 1B):

Inclusion criteria

- Products with documented inferior quality with actual or potential serious implications for the health of patients, such as treatment failures and use in large volumes,
- Medicines that were supplied to many countries (10 or more) and in greater quantities in 2013-2014 to recipient countries by a major donor partner,
- Paediatric formulations,
- Estimated high probability of occurrence of a quality problem (taking into account complexity of manufacture *e.g.* FDC with 2 or more actives, stability of product *e.g.* susceptible to quality deterioration (unstable active pharmaceutical ingredients, liquid dosage forms and suitability of specifications to control potential problems),
- Exposure of patients to the product (way of dispensing and extent of exposed population),
- Seriousness of potential harm (vulnerability of target population, risks related to product's dosage form and route of administration and to therapeutic properties, such as therapeutic index, risk of therapeutic failure, acute versus chronic use, development of resistance),
- Reported cases of SSFFC, and
- Products with five or more prequalified generics hence potential for diversity on the market.

Exclusion criteria

- Medicines deemed to be of assured quality because of production in stringent regulatory systems,
- products with no pharmacopoeial monographs regardless of prequalification status,
- Low risk products as in Annex 1B,
- Products supplied to few countries (5 or less) and in relatively lower quantities,
- Products in bulk packaging and likely to cost more in samples transportation *e.g.* bottles,
- Products with 2 or less prequalified generics, hence reliance on innovator products.

Taking into account the above considerations, and assuming majority of products supplied were prequalified; the following seven (7) medicines were selected for sampling due anticipated availability (Annex 1A) and the outcomes of this risk assessment (Annex 1B):

Monocomponent

- Lamivudine 150 mg or 300 mg tablets
- Efavirenz 600 mg tablets
- Nevirapine 50 mg dispersible tablets

Fixed-dose combinations (FDCs)

- Lamivudine/nevirapine/zidovudine 30/50/60 mg dispersible tablets
- Efavirenz/emtricitabine/tenofovir disoproxil fumarate 600/200/300 mg tablets
- Lamivudine/zidovudine 30/60 mg dispersible tablets
- Lamivudine/zidovudine 150/300 mg tablets

The following eight countries were approached before the final selection of 6 countries (Burkina Faso, Democratic Republic of the Congo, Nigeria, Rwanda, Vietnam and Zambia) was made:

- Nigeria – included in the last (2007) study.
- Vietnam - part of laboratory evaluation and supplied with most of targeted products by donors.
- Zimbabwe – part of recently prequalified laboratory evaluation, and part of ZaZiBoNa[17] project.
- Democratic Republic of the Congo – included in the last (2007) study.
- Zambia – included in the last (2007) study + part of ZaZiBoNa project.
- Burkina Faso - supplied with most of targeted products by donors and included in other non-ARV studies.
- Rwanda – recommended in the 2007 study for future study.
- Senegal – recommended in the 2007 study for future study.

[17] ZaZiBoNa Project – pilot project on worksharing and joint medicine dossier review by 4 countries Zambia, Zimbabwe, Botswana and Namibia.

NMRAs of the selected countries were contacted and requested to cooperate within the survey and to identify a focal person for this survey and notify him/her to the WHO-PQ focal point.[18] Appropriate arrangements with the NMRAs in the selected countries regarding cooperation and reimbursement of activities done by NMRAs were agreed to.

Nominated focal persons in countries will be responsible for:

- Identification of the appropriate sampling sites and expected availability of selected products,
- Preparation of a national sampling plan (see Annex 2),
- Organization of sampling in the country and transportation of samples to the pre-specified testing laboratories,
- Participation in analysis of outcomes of quality monitoring of products and recommending corrective actions in the country, if necessary.

Before national sampling plans are finalized and sampling starts, a meeting was organized by PQT with participation of focal persons from the selected countries to

- Explain the quality survey,
- Discuss and, if needed, modify the survey protocol to reflect local conditions,
- Discuss availability and quality of selected medicines in the respective countries and finalize national sampling plans,
- Provide detailed instructions for collection and transportation of samples,
- For countries included in previous ARV survey of 2007, indicate any measures that have been planned or implemented following study recommendations.

4.2 Survey period

The preparatory work on the survey started in March 2015. The survey should be completed in the middle of 2016 as indicated in Table 1.

Table 1 Timeframe for the quality survey

Activity	Timeframe	Responsibility
• Search on availability of medicines included in the protocol • Preparation of draft protocol • Selection of countries and medicines to be included in the quality survey	March – April 2015	PQT PQT PQT
• Finalization of survey protocol	May 2015	PQT
• Sending of letters to NMRAs in selected countries • Preparation of APWs with NMRAs to cover national expenditures	May - June 2015	PQT
• Selection of laboratories for performance of tests	May 2015	PQT
• Organization of meeting with focal persons from selected countries	July 2015	PQT in cooperation with WHO office in the country where meeting takes place
• Collection of samples by NMRAs	July – November 2015	NMRAs
• Testing of samples by selected laboratories	July 2015 – February 2016	Testing laboratories
• Compilation and evaluation of results	February – June 2016	PQT
• Organization of meeting with the participating countries to discuss final results and actions needed	March 2016	PQT in cooperation with WHO office in the country where meeting takes place
• Publication of report	June 2016	PQT

4.3 Selection of sample collection sites – the sampling frame

No samples will be collected from the informal sector *i.e.* outside the approved distribution system.

To obtain limited information about the quality of products as supplied by manufacturers and reduce the influence of inappropriate transport, storage conditions and control, samples will be collected at the first and

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second levels of distribution chain, *e.g.* in central medical stores, NGO central stores, warehouses of importers or major distributors or other facilities supplied directly within various programmes as well as treatment/retail sites. This provides the advantage of detecting quality issues before the products reach the patient. Samples collected close to the point of sale to patients in the supply chain may be influenced by distribution and storage conditions, such as high temperatures and close to expiry.

Due to funding limitations the ratio of first level to second level facilities to be included should be 2:3 (*i.e.* 40% to 60% respectively). In addition, following previous studies, two (2) geographical regions should be targeted for both levels preferably with equal distribution of sites between regions.

The following guidance may be used for selection of geographical regions:

- Regions where more sites for sampling will be available,
- Regions with at least one level 1 site,
- Regions with conditions (*e.g.* climatic, storage etc.) that are likely to affect the product *e.g.* stability; and/or
- Locations with likely presence of poor quality product.

Samples will therefore be collected from the following levels of the distribution chain:

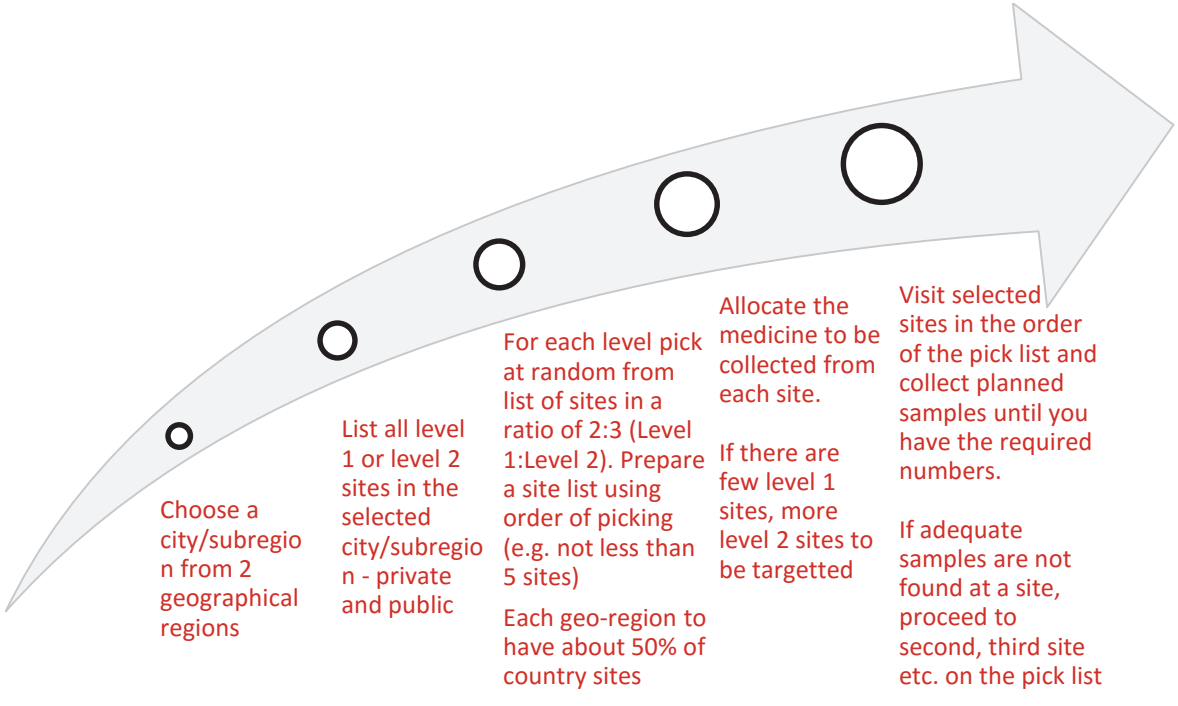
- Level 1 (central) 40% of sites – highest level of the distribution system *i.e.* importers, central medical stores, manufacturers and central stores for non-governmental organizations,
- Level 2 (Outlets) 60% of sites - wholesalers, regulated retailers as well as dispensing facilities and treatment centres, in both private and public sectors.

Focal persons in selected countries will identify sites where medicines selected for this survey can be collected and prepare the lists of products which are potentially available in these sites for the selected medicines. These lists will be discussed in the meeting with focal persons.

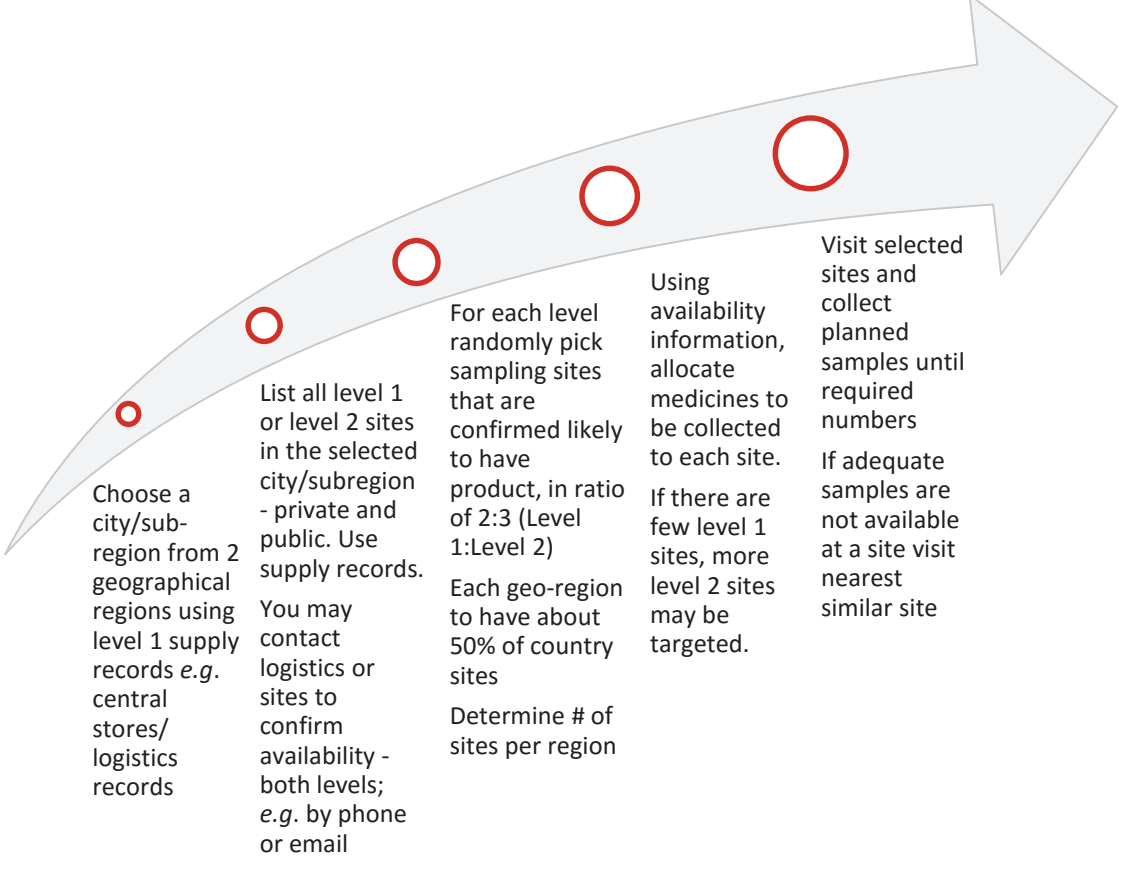
About 42 collection sites in 6 countries *i.e.* 7 per country from official procurement and treatment centres, both private and public are anticipated.

4.4 Sample collection

From the list of each country's potential sites the following two sampling logic options should be used to choose the final targets.



Site Selection – Option 1



Site Selection – Option 2

For the purposes of this project, a sample means an item collected from each medicine's presentation (identified by the name, content of APIs, dosage form, strength, batch number and manufacturer) at the same collection site. Therefore a product of the same name, content of APIs, the same dosage form, strength, batch and from the same manufacturer collected in two different sites represents two samples.

Samples will be collected by the staff of the NMRA in the respective country as per schedule in section 4.2. WHO-PQT will provide direct funding to the NMRA towards costs for local expenditures. This will be included in a signed agreement.

The number of dosage units to be collected per sample is specified for each medicine in the national sampling plan template (Annex 2). As only unopened original packages shall be collected, the number of units per sample will be dependent on the pack size. If there are less tablets/capsules or containers (as the case may be) available for the particular batch than requested, the sample should not be collected and another batch should be selected.

A detailed national sampling plan will be prepared for each country by the focal person in the NMRA in cooperation with WHO-PQT (Annex 2). The focal person in each country will arrange for training of collectors to be familiar with the national sampling plan and instructions.

In general the following information shall be included in the national sampling plan:

- Identification of the country and the person responsible for sampling
- Names and addresses of the sites, where samples shall be collected
- Identification of medicines to be collected (active pharmaceutical ingredients by INNs, dosage form, strength, potential manufacturers following official registers, number of batches expected to be collected in each site and number of units to be collected per batch of each medicine)
- Maximum number of samples collected per country
- Detailed instructions for collecting samples (see below).

Number of dosage units of selected medicines to be collected should allow for:

- conducting the agreed tests,
- possible confirmatory testing due to out-of-specification investigations, and
- retention samples.

To fulfil the objectives of this quality survey, samples from as many manufacturers as possible should be collected. The following principles should be applied when selecting products for sampling:

- Only dosage forms and strengths specified in the list of medicines for sampling will be collected.
- If there are more strengths or pack sizes per medicine recommended within the project and available for the particular product in the country, it is sufficient to collect one of them. In principle, the higher strengths and biggest pack sizes should be collected.
- FIVE (5) samples of each product should be collected for each country, except for Burkina Faso where, due to unavailability of nevirapine 50 mg dispersible tablets, SIX (6) samples of each product may be collected. Each country will therefore collect not more than 35 product samples.
- The ratio of 2:3 for samples from level 1: level 2 should be respected and particularly not more than TWO level 1 samples for each product.
- If more than 1 batch of a product is available, the older batch should be collected, provided there is at least six months remaining to expiry.
- Samples of products from various manufacturers should be collected rather than several batches produced by one manufacturer. If many brands are available for sampling:
    - the most unlikely quality assured products should be collected, but
    - it is not necessary to collect samples from products manufactured in countries with stringent regulatory systems.

Sampling will be recorded using the sample collection form (Annex 3). Whenever the required information is not available, it should be indicated by "NA" in the appropriate space on the sample collection form, where also any abnormalities should be recorded.

During sample collection the storage conditions at the site should be evaluated and described in the sample collection form (see Annex 3).

Collected samples should be taken to the NMRA as quickly as possible and the time period when they are kept outside the conditions recommended by the manufacturer should be short.

In case manufacturer's batch certificates of analysis are available, a copy should be collected with the samples and kept with the sample collection form. Any other available results of analysis of the collected batch (pre- or post-shipment, testing by procurers or NMRAs) should also be collected with samples and kept with the sample collection form.

Instructions for sample collection:

- The time period, within which samples should be collected in the countries and the deadline for sending the last sample to the testing laboratory, should be followed.
- The minimum quantity of sample per batch and number of batches to be collected from each collection site for each selected medicine as indicated in the Sampling Plan should be followed. Note that there should not be a mix-up with batches, all units of one sample must be of the same batch. In the case that in a collection site the required number of packages of the same batch is not available, sample of that particular medicine is not collected.
- Samples collected should have at least six months remaining to expiry.
- Only unopened original packages should be collected.
- The medicine samples should not be taken out of the original primary packaging and outer containers (although removal from large secondary packs may be appropriate). Containers such as bottles should not be opened.
- The medicine labels and package leaflets should not be removed or damaged. This includes product information *i.e.* patient information leaflet and professional information leaflet.
- In order to avoid confusion, each sample should be identified by a unique Sample Code (for coding system see the Sample Collection Form, Annex 3) specified in the Sample Collection Form as well as on all the original packages belonging to the respective sample. Packages belonging to one sample and Sample Collection Form will be kept together (*e.g.* blisters inserted in a dedicated envelope marked with the appropriate sample code and trade name of the product).
- The survey interview form should be completed onsite and submitted to WHO contact point separately (Annex 4).
- The samples should be collected and kept under controlled storage conditions, as per label requirements.

If needed, appropriate arrangements should be made with treatment centres to ensure that there is no shortage due to collection of samples (*e.g.* requesting for replacements of medicines or payment for collected samples).

4.5 Storage and dispatch of samples

- The samples should be kept in the original packaging and under storage conditions specified on the label.
- For transportation, all samples should be packaged adequately and transported in such a way as to avoid damage and contamination. Any residual space in the container should be filled with a suitable material.
- Product information should be submitted with the sample to the designated laboratory for forwarding to WHO– another study of the product information will be conducted from WHO and reported separately.
- A packing list should be prepared listing all samples in the shipment (product names, manufacturers, batch numbers and exact quantities). If more than one parcel/box is used, a packing list should be prepared showing the contents of each parcel/box.

- Each shipment should be accompanied by the following documents (further referred to as "accompanying documents"):
  - A sample covering letter,
  - Packing list(s),
  - Copies of sample collection forms and,
  - Copies of manufacturer's and any other available certificates of analysis, if accessible (in case that search for these certificates would delay dispatch of samples, they may be sent to testing laboratories and WHO contact point separately later).
- Samples with the accompanying documents should be sent by the NMRA straight to the assigned testing laboratories by courier service.
  - Costs for shipment will be paid directly by the NMRA from the funds provided for this survey by WHO-PQT as per agreement for performance of work (APW).
  - For each shipment it should be clearly indicated that 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. Low price just for customs purposes should be indicated to avoid problems with the customs clearance.
  - As there may be slight differences among storage conditions for products with the same API from different manufacturers, the following transportation conditions should be requested from the courier service:
    - Freezing of all samples has to be avoided
    - Tablets and Solutions/liquids should be kept below 25°C
- The contact points in laboratories and in WHO should be informed about the shipment and the tracking number as provided by the courier service.

4.6 Records on collection and dispatch of samples

Records on collection and dispatch of samples are the following:

- National sampling plan,
- Site product information survey form (Annex 4),
- Accompanying documents (covering letter, packing list(s), product information, copies of sample collection forms and, copies of manufacturer's and any other available certificates of analysis, if accessible),
- Shipment documents.

Three sets of these records should be prepared:

- One set of records is retained by the NMRA,
- The Second set, including the Site Product Information survey form, should be sent to WHO contact point,
- The Third set should be sent together with samples to the contact points in the respective laboratories. It is not necessary to send national sampling plan to each testing laboratory.

4.7 Testing laboratories

Four WHO prequalified quality control laboratories will be used for testing of samples collected within this survey.

Table 2 shows the division of samples among the selected laboratories.

Table 2 Laboratories performing quality testing

Testing laboratory	Address	Medicine(s) to be tested
InphA Laboratories GmbH	Emil-Sommer Str. 7 28329 Bremen Germany	Efavirenz/emtricitabine/tenofovir disoproxil fumarate 600/200/300 mg tablets
Medicines Control Authority of Zimbabwe, National Quality Control Laboratory (NQCL), Harare, Zimbabwe	106 Baines Avenue Harare Zimbabwe	Lamivudine 150 mg or 300 mg tablets
National Institute of Drug Quality Control (NIDQC), Viet Nam	48 Hai Ba Trung Street, Hanoi, Hoan Kiem District, Viet Nam	Lamivudine/nevirapine/zidovudine 30/50/60 mg dispersible tablets Nevirapine 50 mg dispersible tablets
Tanzania Food and Drugs Authority (TFDA), Quality Control Laboratory, Tanzania	PO Box 77150, Nelson Mandela Road, EPI-Mabibo External, Dar es Salaam, United Republic of Tanzania	Efavirenz 600 mg tablets Lamivudine/zidovudine 150/300 mg tablets Lamivudine/zidovudine 30/60 mg dispersible tablets

WHO Prequalification of Medicines Team will cover all testing costs.

In addition to providing the testing data, some aspects of the quality of service provided by the selected laboratories will be evaluated including the following:

- Clarity of quotations, including understanding of testing required.
- Clarity of responses to queries and turnaround time for requests (from quotation to submission of final report)
- Availability and/or capacity to perform requested tests.
- Performance vs submitted quotations and APW.
- Evaluation of method suitability before use – method transfer/verification/validation
- Details provided in the comprehensive analyses report *e.g.* including discussions of uncertainty of measurements (where applicable), assay always in triplicate, related substances in duplicate, checking of reference solution using independently prepared solution of the reference standard.
- Details provided in the certificates of analyses. Including details of any repeat analyses.
- Handling of OOS results and communication thereof with WHO-PQT.
- Optimal use of supplied samples and standards.

4.8 Tests to be conducted

Laboratory testing of all collected samples will be performed according to the testing protocol agreed with the testing laboratories. In principle, the following tests are included:

- Appearance
- Labelling
- Identity
- Assay

and depending on formulation and specifications the following additional tests;

- Test for related substances
- Dissolution
- Disintegration time
- Uniformity of dosage units
- Fineness of dispersion
- Water content

4.9 Test methods and specifications

Testing methods and specifications are compendial methods of *The International Pharmacopoeia*, the British Pharmacopoeia or the United States Pharmacopeia. When a monograph is available in more pharmacopoeias, the ability of the respective specifications and methods to reveal quality problems will be considered and the appropriate monograph selected accordingly for easiness of testing and cost. In some cases tests from one or more pharmacopoeias may be used to provide a more complete picture about the quality of a particular medicine. Detailed testing protocol is attached as Annex 5.

Whenever a prequalified product on testing is found to be out of specifications, attempts to use the validated method accepted by WHO-PQT will be used.

4.10 Receipt and testing of samples by a testing laboratory

The testing laboratories should ensure that:

- Each sample will be inspected to ensure that the labelling is in conformance with the information contained in the sample collection form. An electronic databank (photos of dosage forms *e.g.* tablets and packaging including labelling) is required and all original product information should be submitted to the WHO contact point.
- Samples are stored according to the respective label requirements.
- Quality testing is conducted in line with this protocol, with the agreed testing protocol and in compliance with WHO standards recommended for quality control laboratories.[19] Samples containing the same API/s in the same dosage form are tested as a series.
- Certificate of Analyses and Analytical Test Reports (Annex 6) are prepared. In the case that non-compliant results are found and confirmed after application of a laboratory out-of-specification procedure, they are reported without delay to the WHO contact point.
- Records of testing of each sample, accompanying document/s and retention samples are kept for at least six months if the sample complied with the analytical test requirements, or for at least one year or until the expiry date (whichever is longer) if it did not comply.

5. Data management, analysis and publication

Any non-compliant result found in the survey should be communicated without delay and investigated with the respective NMRA and manufacturer.

For any sampled prequalified products a simple verification, in order to identify potentially falsely labelled/falsified/counterfeited products, will be made with manufacturers on authenticity of production details (Batch number, Dates of manufacture/expiry, Country of supply).

The testing results will be provided to all NMRAs involved in the survey. The outcomes of the survey will be discussed by national authorities and WHO, and corrective actions, if necessary, will be recommended. The responsibility to take any relevant measures in the countries lies with the respective NMRAs.

Outcomes and the report from the survey will be published by WHO.

[19] Good practices for pharmaceutical quality control laboratories. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Forty fourth report. Geneva, World Health Organization. WHO Technical Report Series, No. 957, 2010, Annex 1. http://www.who.int/prequal/info_general/documents/TRS957/GPCL_TRS957_Annex1.pdf

Annex 1A to Survey protocol:

Most supplied ARV medicines funded by The Global Fund in 2013-14

Note: Products shaded grey were selected

Product	Description	Potential reason for inclusion	Potential reason for exclusion
Abacavir	20 mg/ml | oral liquid	Paediatric	Supplied to 5+ countries, cost of sample transportation
Abacavir	60 mg | dispersible tablets	Paediatric	Supplied to 5+ countries, 2 generics prequalified
Abacavir	300 mg | tablets	Supplied to 10+ countries	
Abacavir+lamivudine - FDC	600 mg+300 mg | tablets		No pharmacopoeia reference monograph
Abacavir+lamivudine - FDC	60 mg+30 mg | tablets	PQ donor priority product, Paediatric	No pharmacopoeia reference monograph
Abacavir+lamivudine+zidovudine - FDC	300 mg+150 mg+300 mg | tablets		Supplied to 3 countries only
Atazanavir+ritonavir - FDC	300 mg+100 mg | tablets	PQ donor priority product	No pharmacopoeia reference monograph
Didanosine	125 mg | capsules delayed release		Only 2 countries supplied. Low availability reported in previous study
Didanosine	400 mg | tablets		Supplied to 5 countries only. 2 generics prequalified
Didanosine	200 mg | capsules delayed release		Only 2 countries supplied
Didanosine	25 mg | chewable tablets		Only innovator supplied, 1 generic prequalified
Efavirenz	600 mg | tablets	Supplied to 20+ countries	
Efavirenz	200 mg | tablets	Supplied to 15+ countries	Same suppliers as higher (600 mg) strength, 1 generic prequalified
Efavirenz	50 mg | capsules	Paediatric, Supplied to 10+ countries	
Efavirenz+emtricitabine+tenofovir disoproxil fumarate - FDC	600 mg+200 mg+300 mg | tablets	Complex FDC prequalified in last 24-36 months	Supplied to 5+ countries
Emtricitabine+tenofovir disoproxil fumarate - FDC	200 mg+300 mg | tablets	7 generics prequalified	Supplied to 5+ countries
Lamivudine	150 mg or 300 mg | tablets	Supplied to 15+ countries	
Lamivudine	10 mg/ml | oral liquid	Paediatric, Supplied to 15+ countries	Cost of sample transportation
Lamivudine+nevirapine+zidovudine - FDC	150 mg+200 mg+300 mg | tablets	Supplied to 25+ countries	
Lamivudine+nevirapine+zidovudine - FDC	30 mg+50 mg+60 mg | dispersible tablets	Paediatric, PQ donor priority product, Supplied to 20+ countries	
Lamivudine+tenofovir disoproxil fumarate - FDC	300 mg+300 mg | tablets	5 generics prequalified	No pharmacopoeia reference monograph
Lamivudine+zidovudine - FDC	30 mg+60 mg | dispersible tablets	Paediatric, Supplied to 15+ countries	
Lamivudine+zidovudine - FDC	150 mg+300 mg | tablets	Supplied to 20+ countries	
Nevirapine	200 mg | tablets	Supplied to 25+ countries	
Nevirapine)	10 mg/ml | oral liquid	Paediatric, Supplied to 10+ countries	Sample transportation costs
Nevirapine	50 mg | dispersible tablets	Paediatric	Supplied to 5+ countries
Tenofovir disoproxil fumarate	300 mg | tablets	Supplied to 10+ countries	
Zidovudine	300 mg | tablets	Supplied to 10+ countries, 7 generics prequalified	Included in 2007 study
Zidovudine	10 mg/ml | oral liquid	Paediatric, Supplied to 10+ countries, 6 generics prequalified	Sample transportation costs
Zidovudine	100 mg | capsules		Supplied to 3 countries only

Annex 1B to Survey protocol:

Risk assessment of targeted medicines

Product Generic Name	Strength + Form	Solubility issues?	BCS Class + Basis[20]	Risk assessment of targeted medicines Scale: 0=low risk, 1=medium risk, 2=high risk									Risk Score
				Problem occurrence - probability			Exposure			Potential harm			
				Dosage form manufacture risk - incl. complexity of manufacture (Modified Release = 2)	Stability	Efficacy - BCS Classification of API (0 = BCS 1, 1 =BCS 3 or 1/3, 2 = BCS 2 or 4)	Specifications controlling potential problems	Way of dispensing	Extent of exposed population	Vulnerability of target population	Dosage form and administration	Therapeutic properties (therapeutic index, risk of therapeutic failure, acute vs chronic use, resistance)	Max = 16
Efavirenz	600 mg | tab	Efavirenz	4 - Efavirenz	1	0	2	2	0	2	2	0	2	11
Efavirenz	50 mg | capsule	Efavirenz	4 - Efavirenz	0	0	2	2	0	2	2	0	2	10
Efavirenz+Emtricita-bine+Tenofovir -FDC	600 mg+200 mg+300 mg | tab	Efavirenz + Tenofovir	4 - Efavirenz	1	0	2	2	0	2	2	0	2	11
Lamivudine (3TC)	10 mg/ml | oral liquid	No	3 - Lamivudine	0	0	1	2	1	2	2	1	2	11
Lamivudine (3TC)	150 mg or 300 mg | tab	No	3 - Lamivudine	1	0	1	1	0	2	2	0	2	9
Lamivudine+nevira-pine+zidovudine -FDC	150 mg+200 mg+ 300 mg | tab	Nevirapine	2 - Nevirapine	2	0	2	2	0	2	2	0	2	12
Lamivudine+nevirapine+ zidovudine - FDC	30 mg+50 mg+60 mg | dispers tab	Nevirapine	2 - Nevirapine	2	0	2	2	0	2	2	0	2	12
Lamivudine+zidovudine - FDC	30 mg+60 mg | dispers tab	No	3 - Lamivudine	2	0	1	1	0	2	2	0	2	10
Lamivudine+zidovudine - FDC	150 mg+300 mg | tab	No	3 - Lamivudine	1	0	1	1	0	2	2	0	2	9
Nevirapine (NVP)	200 mg | tab	Nevirapine	2 - Nevirapine	0	0	2	0	0	2	2	0	2	8
Nevirapine (NVP)	50 mg | dispers tab	Nevirapine	2 - Nevirapine	1	0	2	1	0	2	2	1	2	11
Tenofovir disoproxil fumarate (TDF)	300 mg | tab	Tenofovir	3 - Tenofovir	0	0	1	0	0	2	2	0	2	7

[20] WHO PQT Medicines: General Notes on Biopharmaceutics Classification System (BCS)- based Biowaiver Applications, https://extranet.who.int/prequal/sites/default/files/documents/35%20Biowaiver%20general_Nov2014.pdf (accessed 14 March 2017)

Annex 2 to Survey protocol:
National Sampling Plan

Survey of the quality of selected antiretroviral medicines circulating in selected countries

Country: .....

Focal Person: .....

MEDICINES TO BE COLLECTED (please, focus only on specified dosage forms and strengths, if more strengths are available for the particular product, it is not necessary to collect all of them):

- Lamivudine 150 mg tablets or Lamivudine 300 mg tablets
- Efavirenz 600 mg tablets
- Nevirapine 50 mg dispersible tablets
- Lamivudine/nevirapine/zidovudine 30/50/60 mg Dispersible tablets
- Efavirenz/emtricitabine/tenofovir disoproxil fumarate 600/200/300 mg tablets
- Lamivudine/zidovudine 30/60 mg Dispersible tablets
- Lamivudine/zidovudine 150/300 mg tablets

NAMES AND ADDRESSES OF THE SITES, WHERE SAMPLES SHALL BE COLLECTED (first and second level of distribution chain, e.g. in central medical stores, NGO central stores, warehouses of importers; and treatment sites):

	Facility name	**Address**	**Facility type** **1.** Private /public **2.** CMS /NGO /importer/… **3.** Treatment site /Hospital /Clinic
1.			
2.			
3.			
4.			

NUMBER OF SAMPLES TO BE COLLECTED PER PRODUCT:
In principle, **FIVE samples should be collected for each of the 7 selected products in each country**.

TOTAL NUMBER OF SAMPLES PER COUNTRY:
Total number of samples per country **should not exceed 35 samples**.

NUMBER OF UNITS TO BE COLLECTED PER SAMPLE:
Numbers of units to be collected per sample are **specified for individual medicines in the form below**.

SAMPLING RECORD

Medicine Dosage form	Strength	Minimum no. of units to be collected per sample	Manufacturer	Sampling site	Batch no.	Pack size	No. of units collected per sample	Product supplied with professio-nal and patient information leaflet? (Yes/No)	Sample code
Lamivudine tablets	150 mg OR 300 mg	100 tablets							
Efavirenz tablets	600 mg	100 tablets							
Nevirapine dispersible tablets	50 mg	100 tablets							
Lamivudine / nevirapine /zidovudine tablets	30/50/60 mg	100 tablets							
Efavirenz / emtricitabine / tenofovir disoproxil fumarate tablets	600/200/300 mg	100 tablets							
Lamivudine / zidovudine tablets	30/60 mg	100 tablets							
	150/300 mg	100 tablets							

INSTRUCTIONS FOR COLLECTORS:

- An item collected from a medicine (identified by the name, content of APIs, dosage form, strength, batch number and manufacturer) at the same collection site is called a sample. **All dosage units of one sample must be of the same batch**, there should not be a mix-up with batches. In the case that in a collection site the required number of packages of the same batch is not available, sample of that particular medicine should not be collected from that site.
- **Only dosage forms and strengths specified** in the list of medicines for sampling should be collected.
- If there are more strengths or pack sizes per medicine recommended within the project and available for the particular product in the country, it is sufficient to collect one of them. In principle, the **higher strengths** and biggest pack sizes should be collected.
- **Samples of products from various manufacturers should be collected** rather than several batches produced by one manufacturer. If many brands are available for sampling:
  - the most unlikely quality assured products should be collected,
  - it is not necessary to collect samples from products manufactured in countries with stringent regulatory systems.
- Samples collected should have **at least six months remaining to expiry**. Products with a shorter period remaining to expiry date should not be collected.
- **Only unopened original packages should be collected**.
- Medicine **samples should not be taken out of the original primary packaging or outer containers** (Removal of blisters from large secondary packs may however be appropriate). Containers such as **bottles should not be opened**.
- **Sampling should be recorded using the sample collection form** (Annex 3). Whenever the required information is not available, it should be indicated by "NA" in the appropriate space on the sample collection form. Any abnormalities should be recorded.
- Each sample should be identified by a **unique sample code** (for coding system see the sample collection form, Annex 3) **specified in the sample collection form as well as on all the original packages belonging to the respective sample** (legible and not covering basic sample information). Packages belonging to one sample and sample collection form should be kept together (e.g. blisters inserted in a dedicated envelope marked with the appropriate sample code and trade name of the product).
- During sample collection the **storage conditions at the site should be evaluated** and described in the sample collection form (see Annex 3). The **date when the batch sampled was received at the sampling site** should be established and recorded in the sample collection form, with relevant documentary evidence, if available e.g. copy of delivery note, receipt etc.
- Copies of manufacturer's batch **certificates of analysis** should be collected with samples, if available, and kept with the sample collection form. Any other available results of analysis of the collected batch (pre- or post-shipment, testing by procurers or NMRAs etc.) should also be collected with samples and kept with the sample collection form. In case that the search for these certificates would delay dispatch of samples, they may be sent to testing laboratories and WHO contact point separately later.
- The **samples should be collected and kept under controlled storage conditions**, as per label requirements. Collected samples should be taken to the NMRA as quickly as possible and the time period when they are kept outside the conditions recommended by the manufacturer should be short.
- Samples should be collected in all the countries involved during the period July 2015 to November 2015 and the **deadline for sending the last sample to the testing laboratories is 31st November 2015**.
- For the instructions for shipment of samples to the testing laboratories, please see Section 4.5 of the protocol.

Annex 3 to Survey protocol:
Sample collection form*

Survey of the quality of selected antiretrovirals circulating in selected countries

Country: ..... Sample code: .....
(Country code/product abbreviation/sequence number/sampling date ddmmyy)**

Name of location/place where sample was taken:.....

.....

Address (with telephone, fax number and email address, if applicable):.....

.....

Organization and names of people who took samples:

1. .....

2. .....

Product Trade name of the sample (if applicable): .....

Name of active pharmaceutical ingredient(s) (INN) and strength:

.....

Dosage form: .....

Package size, type and packaging material of the container: .....

.....

Batch/lot number: .....

Date of manufacture: ..... Expiry date: .....

Regulatory status in the country, registration number and date of registration, if applicable: .....

.....

Name and address of the manufacturer: .....

.....

Quantity collected (number of tablets):

.....

Product information – label, information leaflet (Patient and Professional) included Yes / No

Initialize first page:

** **Country codes**: Burkina Faso = BF, Democratic Republic of the Congo = DRC, Nigeria = NG, Rwanda = RW, Senegal = SE, Vietnam = VN, Zambia = ZM.
Medicines abbreviations: Lamivudine tablets = LAT, Efavirenz tablets = EFV, Nevirapine tablets = NEV, Lamivudine/Nevirapine/Zidovudine tablets = LNZ, Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate tablets = TEE, Lamivudine/Zidovudine tablets = LZT
Sample code system can be extended to be appropriate for a particular country collection system.

Product name: ..... **Sample code: .....**

Date the batch was received at the location:

.....

Storage conditions at the sampling site:

Conditions controlled: ☐ Yes ☐ No

Temperature and humidity at the place where the sample was stored (at the time of sample collection):

.....

.....

Abnormalities, remarks, observations:

.....

.....

.....

.....

.....

.....

.....

Date:.....

Signature of person(s) taking samples

Name, Designation and Signature of representative of the establishment where sample(s) was taken

1. .....

2. ....

Note: Samples collected must remain in their original primary packaging, intact and unopened

Annex 4A to Survey protocol:

Questionnaire for the Survey on WHOPAR and ARV Product Information

For every ARV treatment centre, at least one treatment staff (Physician/Health officer/Nursing) and one dispensing staff (Pharmacist/Druggist) should be interviewed.

Respondent (please indicate):

- ART treatment centre (Physician/Health officer/Nursing) staff ☐
- Pharmacist/Druggist ☐
- Service at the current or previous ART treatment centre (please indicate): ☐

.....

1. Most common source of medical information on ARTs for the staff of the treatment centre: (choose max of 2)

   Product information found in the product packs ☐

   Hospital formularies ☐

   WHO or national treatment guidelines ☐

   Product information from internet ☐

   Product information from PQ website ☐

   Product information from U.S. FDA/EMA website ☐

   Other, please specify: ☐

   .....

2. Do you have internet access at the treatment centre/Pharmacy? Y /N

3. Are you aware of the product information (SmPC, PIL) published on the WHO Prequalification website for products prequalified by WHO- also known as WHO public assessment report (WHOPAR)? (Please choose one:)

   Yes ☐

   I was not aware of WHOPARs ☐

   I'm aware of WHOPAR but never used it ☐

4. How frequently do you visit the WHOPAR INFORMATION pages on the WHO prequalification website?

   Every day or with every patient sessions ☐

   Once in week ☐

   Once in a month ☐

   Rarely ☐

5. In your view, is there any aspect of the WHOPAR that may need to be improved? Please state:

   .....

   .....

6. What other information source do you use to satisfy your information need on the products that you may prescribe/dispense? Please state:

.....

.....

Product information for the health professionals (prescribing information) - (Q7-8)

7. In your view and experience, the extent of medical information (for health professionals) included in ART product packs (choose one):
   - Contain complete information that is sufficient for my day to day information need ☐
   - Contain reasonable information but in some cases I need to refer to other information sources available to me ☐
   - Does not contain adequate information as a result mostly I depend on other information source ☐

8. What sort of information do you think the product information that you find with the product pack lacks? Please indicate:

.....

.....

.....

Product information for the patient (Q9-11)

9. In your experience and view, information for the patient included in the product pack: (choose all that apply)
   - Contain complete information and are used as primary source of information by the patient ☐
   - Contain reasonable information but some patients may demand additional information ☐
   - Does not contain adequate information; as a result patients usually depend on additional information provided by the ART team ☐
   - Are easily readable and understandable ☐
   - Are of little use since they are not written in local language ☐

10. In your view and experience, the impact of patient information leaflets (included in the product pack) on appropriate dosing and treatment compliance has been (choose one):
   - High ☐
   - Moderate ☐
   - Minimal ☐

11. What sort of information do you think the patient information leaflets that you find with the product packs lack? Please indicate:

    .....

    .....

    .....

12. With respect to the patient information leaflet or prescribing information for the health professionals, what other shortcomings for example in format, readability or language of do you encounter?

    .....

    .....

    .....

The following questions (Q13-15) are to be responded by dispensing/Pharmacy staff only:

13. Most ARV products received are accompanied with
    - information for health professionals/SmPC as well as with patient information leaflet ☐
    - information for health professional/SmPC alone ☐
    - patient information leaflet alone ☐
    - none of the above ☐
      Please explain:
      .....

14. Information for the health professional/SmPC
    a. Is usually provided to the physicians/nurse on a routine basis as an initiative of the pharmacy staff . ☐

    Please explain how this is done:

    .....

    .....

    b. Is usually provided to the physicians/nurses since they usually ask for copies ☐

15. How do you interpret/implement storage conditions, for example “Do not store above 30°C”
    a. I ensure that the product is always stored at a temperature below 30°C ☐
    b. No special precautions are exercised since the temperature in the Pharmacy is never above 30°C ☐
    c. No special precautions are exercised even though the temperature in pharmacy in most days is above 30°C ☐
    d. Certain excursion to a temperature above 30°C in exceptional cases is acceptable ☐

Annex 4B to Survey protocol:

Questionnaire for assessment of acceptability of selected dispersible paediatric tablet products

For every ARV treatment centre, at least one treatment staff (Physician/Health officer/Nursing) and one dispensing staff (Pharmacist/Druggist) directly involved in the provision of ARV treatment should be interviewed.

This questionnaire has two parts. Part I (General) deals on general aspects of dispersible tablet formulation. Part II (Product specific) deals on a specific product sampled at a given site. One questionnaire for each sampled product should therefore be used.

If no dispersible product is available for sampling in a given site, then only one questionnaire with the Part I (General) needs to be filled in.

For example, if there are 3 dispersible products sampled at a given treatment centre, then six questionnaires should be used (3 for each of the Clinician and Pharmacy personnel)

Please indicate the respondent:

- Clinician ☐
- Pharmacy personnel ☐

Part I: General question on dispersible paediatric tablets

In most cases, instructions for dispersion and administration of dispersible tablets (included in the product pack) are easy and replicable by the patient.

- Agree ☐
- Disagree ☐

When product information for dispersible tablets instructs use of small amount of liquid to disperse the tablets, I usually interpret that as:

- Less than 5ml ☐
- Between 5 and 10ml ☐
- Between 10 and 50ml ☐
- Between 50ml to 100ml ☐

Part II: Product specific questions (please use separate questionnaire for each sampled dispersible product)

Details of the product (please indicate the product name and manufacturer, collection site):

.....

.....

.....

Complaints regarding difficulty to get tablets dispersed in the prescribed amount of liquid and despite stirring:

- Rare or none ☐
- Common ☐
- Very common ☐

Complaints regarding general acceptability of the dispersed product:

- Rare or none ☐
- Common ☐
- Very common ☐

Complaints regarding flavour of the dispersed product:

- Rare or none ☐
- Common ☐
- Very common ☐

Complaints regarding sweetness/bitterness of the dispersed product:

- Rare or none ☐
- Common ☐
- Very common ☐

Other common complaints from target population and care givers, if any:

.....

.....

.....

Annex 5 to Survey protocol:
Testing Protocol

Survey of the quality of selected antiretroviral medicines circulating in selected countries

Product Generic Name	Strength + Form	Reference Pharmacopoeia (unless specified under "Test")	Test	Acceptance Criteria
Efavirenz	600 mg | tablets	USP	Appearance	Description
			Identity	HPLC (done with assay)
			Assay - HPLC	92.0 - 108.0%
			Dissolution - UV	NLT 80% (Q) in 30 minutes
			Uniformity of Dosage Units	By weight variation
Efavirenz + emtricitabine + tenofovir disoproxil fumarate - FDC	600 mg + 200 mg + 300 mg | tablets	Ph. Int.	Appearance	Description
			Identity	HPLC (done with assay)
			Assay - HPLC	90.0 - 110.0% for each API
			Dissolution - HPLC	NLT 80% (Q) in 30 minutes for each API
			Uniformity of Dosage Units	By weight variation
			Water content - Karl Fischer	NMT 50 mg/g
			Related Substances	Tenofovir monosoproxil - NMT 5.0%
Lamivudine	150 mg or 300 mg | tablets	BP	Appearance	Description
			Identity	IR
			Assay - HPLC	95.0 - 105.0%
			Dissolution - UV	NLT 75%(Q) in 45 minutes
			Uniformity of Dosage Units	By weight variation
Lamivudine + nevirapine + zidovudine - FDC	150 mg+200 mg+300 mg | tablets	Ph. Int.	Appearance	Description
			Identity	HPLC (done with assay)
			Assay - HPLC	90.0 - 110.0% for each API
			Dissolution - USP HPLC	Nevirapine ONLY: NLT 75% (Q) in 60 minutes
			Uniformity of Dosage Units	By weight variation
Lamivudine + nevirapine + zidovudine - FDC	30 mg+50 mg+60 mg | dispersible tablets	Ph. Int.	Appearance	Description
			Identity	HPLC (done with assay)
			Assay - HPLC	90.0 - 110.0% for each API
			Uniformity of Dosage Units	By weight variation
			Related Substance - HPLC	As per Pharmacopoeia
			Disintegration test	NMT 3 minutes
			Dissolution - USP HPLC	Nevirapine ONLY: NLT 75% (Q) in 60 minutes
			Fineness of dispersion	A smooth dispersion which passes through a sieve screen with a nominal mesh aperture of 710 µm

Product Generic Name	Strength + Form	Reference Pharmacopoeia (unless specified under "Test")	Test	Acceptance Criteria
Lamivudine + zidovudine - FDC	30 mg+60 mg | dispersible tablets	BP	Appearance	Description
			Identity	TLC + HPLC (done with assay)
			Assay - HPLC	95.0 - 105.0% for each API
			Dissolution - HPLC	NLT 75%(Q) in 45 minutes for each API
			Uniformity of Dosage Units	By weight variation
			Disintegration test	NMT 3 minutes
			Fineness of dispersion	A smooth dispersion which passes through a sieve screen with a nominal mesh aperture of 710 µm
Lamivudine + zidovudine - FDC	150 mg+300 mg | tablets	BP	Appearance	Description
			Identity	TLC + HPLC (done with assay)
			Assay - HPLC	95.0 - 105.0% for each API
			Dissolution - HPLC	NLT 75%(Q) in 45 minutes for each API
			Uniformity of dosage units	By weight variation
Nevirapine	50 mg | dispersible tablets	USP	Appearance	Description
			Identity	IR and HPLC (done with assay)
			Assay - HPLC	90.0 - 110.0%
			Dissolution - UV	NLT 75% (Q) in 60 minutes
			Uniformity of dosage units	By weight variation
			Disintegration test	NMT 3 minutes
			Fineness of dispersion	A smooth dispersion which passes through a sieve screen with a nominal mesh aperture of 710 µm

Annex 6 to Survey protocol:
Content of the Analytical Test Report

Survey of the quality of selected antiretroviral medicines circulating in selected countries

The Analytical Test Report shall in accordance with the Good practices for pharmaceutical quality control laboratories♦ provide at least the following information:

1. Name and address of the laboratory performing the sample testing,
2. Number/code of the Analytical Test Report,
3. Name and address of the originator of the request for testing,
4. Sample code from the sample collection form,
5. Date on which the sample was received,
6. Name of the country where the sample was collected,
7. Sample product name, dosage form, active pharmaceutical ingredients, strength, package size, type and packaging material of primary container,
8. Description of the sample (both product and container),
9. Batch number of the sample, expiry date and manufacturing date, if available,
10. Name and address of the manufacturer,
11. Reference to the specifications used for testing the sample, including the limits,
12. Reference to the reference standards used for quantitative determinations,
13. Results of all the tests performed (**numerical results**, if applicable),
14. Discussion of all the tests performed,
15. Conclusion whether or not the sample was found to be within the limits of the specifications used,
16. Date on which the test was performed, and
17. Signature of the head of the laboratory or authorized person.

♦ Good practices for pharmaceutical quality control laboratories. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Forty fourth report. Geneva, World Health Organization. WHO Technical Report Series, No. 957, 2010, Annex 1.
http://www.who.int/prequal/info_general/documents/TRS957/GPCL_TRS957_Annex1.pdf

Appendix 2 Prequalified products of which samples were collected, with information published by WHO in the list of prequalified medicines/finished pharmaceutical products

International Nonproprietary name (INN)	Dosage form & strength	Applicant (manufacturer)	WHO Reference Number	Date of pre-qualification	Shelf life accepted by PQ (years) initial /current**
Efavirenz	Tablet, Film-coated 600 mg	Cipla Ltd, Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg, Lower Parel, Mumbai, Maharashtra, 400 013, India	**HA352 ***	16 Dec 2008	2 /3
Efavirenz	Tablet, coated 600 mg	Strides Shasun Ltd, Strides house, Opp. IIMB, Bilekahali, Bannerghatta Road, Anekal Taluk, Bangalore, Karnataka, 560 076, India	**HA390 ***	24 Feb 2009	2 /3
Efavirenz	Tablet, Film-coated 600 mg	Hetero Labs Ltd, Unit 3, Survey No 51, Plot No 22-110 IDA, Jeedimetla, Hyderabad, Qutubullapur, Rangareddy District, Andhra Pradesh, 500 055, India	**HA399 ***	01 Jul 2009	2 /3
Efavirenz	Tablet, Film-coated 600 mg	Mylan Laboratories Ltd, R&D Center, Plot No 34-A, ANRICH Industrial Estate, Bollaram, Jinnaram Mandal, Medak District, Telangana, 502 325, India	**HA403 ***	25 Jul 2008	2 /3
Efavirenz	Tablet 600 mg	Aurobindo Pharma Ltd, Plot No 2, Maitrivihar, Ameerpet, Hyderabad, Andhra Pradesh, 500 038, India	**U.S. FDA ANDA 07-7673 2**	n/a	n/a
Efavirenz/ Emtricitabine/ Tenofovir diso-proxil (fumarate)	Tablet, Film-coated 600 mg/200 mg/300 mg	Mylan Laboratories Ltd, R&D Center, Plot No 34-A, ANRICH Industrial Estate, Bollaram, Jinnaram Mandal, Medak District, Telangana, 502 325, India	**HA444**	25 Oct 2010	2 /3
Efavirenz/ Emtricitabine/ Tenofovir diso-proxil (fumarate)	Tablet, Film-coated 600 mg/200 mg/300 mg	Cipla Ltd, Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg, Lower Parel, Mumbai, Maharashtra, 400 013, India	**HA500**	08 Dec 2011	3 /3
Efavirenz/ Emtricitabine/ Tenofovir diso-proxil (fumarate)	Tablet, Film-coated 600 mg/200 mg/300 mg	Hetero Labs Ltd, Unit 5, Survey No 439, 440, 441 & 458 APIIC Formulation SEZ, Polepally Village, Jadcherla (M), Mahaboob Nagar District, Telangana, 509 301, India	**HA538 ***	19 Feb 2014	3 /3

* BF = Burkina Faso, DRC = Democratic Republic of the Congo, NG = Nigeria, RW = Rwanda, ZM = Zambia

✓= complies; ✖= does not comply

International Nonproprietary name (INN)	Dosage form & strength	Applicant (manufacturer)	WHO Reference Number	Date of pre-qualification	Shelf life accepted by PQ (years) initial /current**
Lamivudine	Tablet, Film-coated 150 mg	Hetero Labs Ltd, Unit 3, Survey No 51, Plot No 22-110 IDA, Jeedimetla, Hyderabad, Qutubullapur, Rangareddy District, Andhra Pradesh, 500 055, India	**HA153 ***	29 May 2007	2 /3
Lamivudine	Tablet, Film-coated 150 mg	Cipla Ltd, Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg, Lower Parel, Mumbai, Maharashtra, 400 013, India	**HA353**	29 Sep 2010	3 /3
Lamivudine	Tablet, Film-coated 150 mg	Macleods Pharmaceuticals Ltd, 304 Atlanta Arcade, Marol Church Road, Anheri-Kurla Road, Andheri (E), Mumbai, 400 059, India	**HA424 ***	14 Dec 2012	3 /3
Lamivudine	Tablet, Film-coated 150 mg	Micro Labs Ltd, 27 Race Course Road, Bangalore, Karnataka, 560 001, India	**HA644**	26 Oct 2016	4 /4
Lamivudine	Tablet 150 mg	Aurobindo Pharma Ltd, Unit 3, Survey No 313, Bachupally, Hyderabad, Quthubllaur (M), Rangareddy District, Andhra Pradesh, 500 072, India	**U.S. FDA ANDA 07-7464 a 2**	n/a	n/a
Lamivudine/ Nevirapine/ Zidovudine	Tablet, Film-coated 150 mg/200 mg/300 mg	Mylan Laboratories Ltd, R&D Center, Plot No 34-A, ANRICH Industrial Estate, Bollaram, Jinnaram Mandal, Medak District, Telangana, 502 325, India	**HA426 ***	24 Feb 2009	2 /5
Lamivudine/ Nevirapine/ Zidovudine	Tablet, Dispersible 30 mg/50 mg/60 mg	Mylan Laboratories Ltd, R&D Center, Plot No 34-A, ANRICH Industrial Estate, Bollaram, Jinnaram Mandal, Medak District, Telangana, 502 325, India	**HA433 ***	26 Oct 2009	2 /5
Lamivudine/ Nevirapine/ Zidovudine	Tablet, Dispersible 30 mg/50 mg/60 mg	Strides Shasun Ltd, Strides house, Opp. IIMB, Bilekahali, Bannerghatta Road, Anekal Taluk, Bangalore, Karnataka, 560 076, India	**HA557**	24 Oct 2014	2 /2
Lamivudine/ Nevirapine/ Zidovudine	Tablet, Dispersible 30 mg/50 mg/60 mg	Cipla Ltd, Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg, Lower Parel, Mumbai, Maharashtra, 400 013, India	**U.S. FDA NDA 20-3076 2**	n/a	n/a
Lamivudine/ Zidovudine	Tablet, Film-coated 150 mg/300 mg	Cipla Ltd, Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg, Lower Parel, Mumbai, Maharashtra, 400 013, India	**HA060 ***	30 Nov 2004	2 /3

* BF = Burkina Faso, DRC = Democratic Republic of the Congo, NG = Nigeria, RW = Rwanda, ZM = Zambia

✓= complies; ✖= does not comply

International Nonproprietary name (INN)	Dosage form & strength	Applicant (manufacturer)	WHO Reference Number	Date of pre-qualification	Shelf life accepted by PQ (years) initial /current**
Lamivudine/ Zidovudine	Tablet, Film-coated 150 mg/300 mg	Sun Pharmaceutical Industries Limited, Unit 1 & 2, Ganguwala Village, Paonta Sahib, Sirmour District, Himanchal Pradesh, 173 025, India	**HA286**	11 Aug 2005	2 /3
Lamivudine/ Zidovudine	Tablet, Film-coated 150 mg/300 mg	Strides Shasun Ltd, Strides house, Opp. IIMB, Bilekahali, Bannerghatta Road, Anekal Taluk, Bangalore, Karnataka, 560 076, India	**HA291 ***	30 Jun 2006	2 /3
Lamivudine/ Zidovudine	Tablet, Film-coated 150 mg/300 mg	Mylan Laboratories Ltd, R&D Center, Plot No 34-A, ANRICH Industrial Estate, Bollaram, Jinnaram Mandal, Medak District, Telangana, 502 325, India	**HA392 ***	23 Apr 2008	2 /5
Lamivudine/ Zidovudine	Tablet, Film-coated 30 mg/60 mg	Mylan Laboratories Ltd, R&D Center, Plot No 34-A, ANRICH Industrial Estate, Bollaram, Jinnaram Mandal, Medak District, Telangana, 502 325, India	**HA437 ***	25 May 2009	2 /5
Lamivudine/ Zidovudine	Tablet, Film-coated 150 mg/300 mg	Macleods Pharmaceuticals Ltd, 304 Atlanta Arcade, Marol Church Road, Anheri-Kurla Road, Andheri (E), Mumbai, 400 059, India	**HA459 ***	18 Oct 2011	HDPE – 3 /3 Blister – 2 /2
Lamivudine/ Zidovudine	Tablet, Film-coated 150 mg/300 mg	Hetero Labs Ltd, 7-2-A-2 Hetero Corporate Industrial Estates, Sanathnagar, Hyderabad, Rangareddy District, Telangana, 500 012, India	**HA521**	14 Jun 2013	3 /3
Lamivudine/ Zidovudine	Tablet, Dispersible 30 mg/60 mg	Mylan Laboratories Ltd, R&D Center, Plot No 34-A, ANRICH Industrial Estate, Bollaram, Jinnaram Mandal, Medak District, Telangana, 502 325, India	**HA572 ***	10 Apr 2014	2 /2
Lamivudine/ Zidovudine	Tablet 150 mg/300 mg	Aurobindo Pharma Ltd, Plot No 2, Maitrivihar, Ameerpet, Hyderabad, Andhra Pradesh, 500 038, India	**U.S. FDA ANDA 07-7558 2**	n/a	n/a
Lamivudine/ Zidovudine	Tablet, Dispersible 30 mg/60 mg	Cipla Ltd, Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg, Lower Parel, Mumbai, Maharashtra, 400 013, India	**U.S. FDA NDA 20-2814 2**	n/a	n/a
Nevirapine	Tablet, Dispersible 50 mg	Aurobindo Pharma Ltd, Plot No 2, Maitrivihar, Ameerpet, Hyderabad, Andhra Pradesh, 500 038, India	**U.S. FDA NDA 22-299 2**	n/a	n/a

* Refers to products approved by both WHO and U.S. FDA

** Initial = shelf life approved during the initial PQ procedure for the given product /current = shelf life approved at the time of writing the report (February 2017).

* BF = Burkina Faso, DRC = Democratic Republic of the Congo, NG = Nigeria, RW = Rwanda, ZM = Zambia ✓= complies; ✖= does not comply

Appendix 3 Efavirenz 600 mg tablets – test results

Specifications:

Assay: 92.0-108.0%
Uniformity of dosage units: according to Ph. Int. 5.2 - Uniformity of mass
Dissolution: NLT 80% (Q) in 30 minutes

Country of collection * / sample code	Pack size	Manu–facturer	Manufacturing site	Batch number	Manu-facture date	Expiry date	Sampling site	Type of sampling site / region	Storage conditions at sampling site	Shelf life claimed (years)	PQ current approved shelf life (years)	Registra–tion status	Appearance	Iden-tity	Assay %	Uni-formity of dosage units	Dissolu-tion	Con-clu-sion
BF/ EFV/ 04/ 09112015	30 tablets in plastic bottle	Auro-bindo Pharma Ltd	Bachupally Village, Ranga Reddy, Telangana, India	HG6014 015-A	11 2014	10 2017	Centrale d'Achat des Médicaments Essentiels Génériques et des Consommables médicaux (CAMEG), ZAD Ouagadougou	Importer, level 1, public / Centre	Controlled, 31.1°C, 33.3% RH	3	n/a	Not registered (donation)	Yellow coloured, oval shaped, biconvex film-coated tablets, debossed "D" on one side and "37" on the other side	✓	✓ 97.6	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): 89.6%	✓
BF/ EFV/ 05/ 09112015	30 tablets in plastic bottle	Strides Arcolab Ltd	Suragajakkanahalli, Indlawadi Cross, Anekal Taluk, Bangalore, Karnataka, India	7223320	12 2014	11 2017	Centrale d'Achat des Médicaments Essentiels Génériques et des Consommables médicaux (CAMEG), ZAD Ouagadougou	Importer, level 1, public / Centre	Controlled, 17°C	3	3	Not registered (donation)	Yellow-off white coloured, capsule shaped, biconvex film-coated tablets, plain on both sides	✓	✓ 93.9	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): 95.4%	✓
BF/ EFV/ 06/ 18112015	30 tablets in plastic bottle	Cipla Ltd	Verna, Goa, India	G47587	7 2014	6 2017	Hôpital de jour (HDJ), Banfora	Hospital, level 2, public / Cascades	Not con-trolled	3	3	Not registered (supplied on special permis-sion)	Yellow coloured, capsule shaped, biconvex film-coated tablets, debossed 'EFV' on one side and plain on the other	✓	✓ 95.3	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): 94.4%	✓
BF/ EFV/ 07/ 17112015	30 tablets in plastic bottle	Strides Arcolab Ltd	Suragajakkana-halli, Indlawadi Cross, Anekal Taluk, Bangalore, Karnataka, India	7222277	7 2014	6 2017	Hôpital de jour (HDJ) universitaire de Bobo Dioulasso	Hospital, level 2, public / Hauts-Bassins	Controlled, 26.6°C	3	3	Not registered (donation)	Yellow-off white coloured, capsule shaped, biconvex film-coated tablets, plain on both sides	✓	✓ 99.4	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): 95.4%	✓

* BF = Burkina Faso, DRC = Democratic Republic of the Congo, NG = Nigeria, RW = Rwanda, ZM = Zambia

✓= complies; ✖= does not comply

Country of collection * / sample code	Pack size	Manu–facturer	Manufacturing site	Batch number	Manu-facture date	Expiry date	Sampling site	Type of sampling site / region	Storage conditions at sampling site	Shelf life claimed (years)	PQ current approved shelf life (years)	Registra–tion status	Appearance	Iden-tity	Assay %	Uni-formity of dosage units	Dissolu-tion	Con-clu-sion
DRC/ EFV/ 05/ 27-10-15	30 tablets in plastic bottle	Mylan Laboratories Ltd	Sinnar, Nashik, Maharashtra, India	3037268	3 2015	2 2018	Bolloré Transport & Logistics, Bobozo, Kinshasa	Medical store, level 1, private / Kinshasa	Controlled, 21°C, 56% RH	3	3	Not registered (supplied on special permission)	Yellow-peach coloured, capsule shaped, biconvex film-coated tablets, debossed "M109" on one side and plain on the other	✓	✓ 97.9	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): 95.4%	✓
DRC/ EFV/ 11/ 10-11-15	30 tablets in plastic bottle	Strides Arcolab Ltd	Suragajakkanahalli, Indlawadi Cross, Anekal Taluk, Bangalore, Karnataka, India	7222765	11 2014	10 2017	Centrale d'Achat des Médicaments Essentiels de Lubumbashi (CAMELU), Katanga	Medical store, level 1, NGO / Haut-Katanga	Controlled, 24°C, 52% RH	3	3	Not registered (supplied on special permission)	Yellow-off white coloured, capsule shaped, biconvex film-coated tablets, plain on both sides	✓	✓ 96.2	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): 90.4%	✓
DRC/ EFV/ 23/ 06-11-15	30 tablets in plastic bottle	Strides Arcolab Ltd	Suragajakkanahalli, Indlawadi Cross, Anekal Taluk, Bangalore, Karnataka, India	7221387	4 2014	3 2017	Bureau Diocésain des Oeuvres Médicales (BDOM), Bukavu	Medical store, level 2, NGO / South Kivu	Controlled, 22°C, 60% RH	3	3	Not registered (supplied on special permission)	Yellow-off white coloured, capsule shaped, biconvex film-coated tablets, plain on both sides	✓	✓ 104.1	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): 90.4%	✓
DRC/ EFV/ 25/ 10-11-15	30 tablets in plastic bottle	Strides Arcolab Ltd	Suragajakkanahalli, Indlawadi Cross, Anekal Taluk, Bangalore, Karnataka, India	7222765	11 2014	10 2017	Centrale d'Achat des Médicaments Essentiels de Kisangani (CAMEKIS), Kisangani	Medical store, level 2, NGO / Tshopo	Controlled, 25.3°C, 53% RH	3	3	Not registered (supplied on special permission)	Yellow-off white coloured, capsule shaped, biconvex film-coated tablets, plain on both sides	✓	✓ 97.3	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): 90.2%	✓
DRC/ EFV/ 28/ 10-11-15	30 tablets in plastic bottle	Hetero Labs Ltd	Polepally Village, Mahaboob Nagar, Andhra Pradesh, India	EFZ113026	10 2013	9 2016	Centrale d'Achat des Médicaments Essentiels de Kisangani (CAMEKIS), Kisangani	Medical store, level 2, NGO / Tshopo	Controlled, 23.5°C, 53% RH	3	3	Not registered (supplied on special permission)	Yellow coloured, capsule shaped, biconvex film-coated tablets, debossed with 'H' on one side and '4' on the other side	✓	✓ 98.3	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): 91.2%	✓
NG/ EFV/ 01/ 090915	30 tablets in plastic bottle	Aurobindo Pharma Ltd	Bachupally Village, Ranga Reddy, Telangana, India	EA0603021-A	3 2013	2 2016	Federal Medical Stores, Oshodi, Lagos State (Govt)	Medical store, level 1, public / Lagos	Controlled, 21°C, 52% RH	3	n/a	Registered	Yellow coloured, oval shaped, biconvex film-coated tablets, debossed "D" on one side and "37" on the other side	✓	✓ 96.7	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): 93.3%	✓

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✓= complies; ✖= does not comply

Country of collection * / sample code	Pack size	Manu–facturer	Manufacturing site	Batch number	Manu-facture date	Expiry date	Sampling site	Type of sampling site / region	Storage conditions at sampling site	Shelf life claimed (years)	PQ current approved shelf life (years)	Registra–tion status	Appearance	Iden-tity	Assay %	Uni-formity of dosage units	Dissolu-tion	Con-clu-sion
NG/ EFV/ 02/ 090915	30 tablets in plastic bottle	Cipla Ltd	Verna, Goa, India	G36688	1 2013	12 2015	Federal Medical Stores, Oshodi, Lagos State (Govt)	Medical store, level 1, public / Lagos	Controlled, 21°C, 53% RH	3	3	Registered	Yellow coloured, capsule shaped, biconvex film-coated tablets, debossed 'EFV' on one side and plain on the other	✓	✓ 94.9	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): 87.3%	✓
NG/ EFV/ 09/ 030915	30 tablets in plastic bottle	Mylan Labo-ratories Ltd	Sinnar, Nashik, Maharashtra, India	8019294	12 2013	11 2016	General Hospital, Rigasa, Kaduna State	Hospital, level 2, public / Kaduna	Controlled, 22°C, 51% RH	3	3	Registered	Yellow-peach coloured, capsule shaped, biconvex film-coated tablets, debossed "M109" on one side and plain on the other	✓	✓ 95.2	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): 111.0%	✓
NG/ EFV/ 10/ 030915	30 tablets in plastic bottle	Mylan Labo-ratories Ltd	Sinnar, Nashik, Maharashtra, India	8019294	12 2013	11 2016	General Hospital, Ikara, Kaduna State	Hospital, level 2, public / Kaduna	Controlled, 20°C, 52% RH	3	3	Registered	Yellow-peach coloured, capsule shaped, biconvex film-coated tablets, debossed "M109" on one side and plain on the other	✓	✓ 95.4	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): 104.7%	✓
NG/ EFV/ 17/ 030915	30 tablets in plastic bottle	Strides Arcolab Ltd	Suragajakkana-halli, Indlawadi Cross, Anekal Taluk, Bangalore, Karnataka, India	7221173	3 2014	2 2017	Giwa Hospital Limited, Abakpa Kaduna State (Pvt)	Hospital, level 2, public / Kaduna	Controlled, 22°C, 50% RH	3	3	Registered	Yellow-off white coloured, capsule shaped, biconvex film-coated tablets, plain on both sides	✓	✓ 93.6	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): 92.5%	✓
RW/ EFV/ 002/ 18.nov.2015	30 tablets in plastic bottle	Hetero Labs Ltd	Polepally Village, Mahaboob Nagar, Andhra Pradesh, India	EFZ114008 A	7 2014	6 2017	Rwamagana Hospital, Rwamagana	Hospital, level 2, public / Eastern	Controlled, 25°C	3	3	Not registered (central supply to govern-ment centres)	Yellow coloured, capsule shaped, biconvex film-coated tablets, debossed with 'H' on one side and '4' on the other side	✓	✓ 92.8	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): 97.7%	✓
RW/ EFV/ 003/ 20.nov.2015	30 tablets in plastic bottle	Micro Labs Ltd	Verna, Goa, India	EUAG127	6 2015	5 2017	Medical Procurement and Production Division (MPPD), Kigali	Medical store, level 1, public / Kigali	Controlled, 25°C	2	n/a	Not registered (central supply to govern-ment centres)	Yellow coloured, oval shaped, biconvex film-coated tablets, debossed "O" on one side and plain on the other	✓	✓ 97.8	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): 104.0%	✓

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Country of collection * / sample code	Pack size	Manu–facturer	Manufacturing site	Batch number	Manu-facture date	Expiry date	Sampling site	Type of sampling site / region	Storage conditions at sampling site	Shelf life claimed (years)	PQ current approved shelf life (years)	Registra–tion status	Appearance	Iden-tity	Assay %	Uni-formity of dosage units	Dissolu-tion	Con-clu-sion
RW/ EFV/ 001/ 18.nov.2015	30 tablets in plastic bottle	Hetero Labs Ltd	Polepally Village, Mahaboob Nagar, Andhra Pradesh, India	EFZ113035A	12 2013	11 2016	Kayonza District Pharmacy	Pharmacy, level 2, public / Eastern	Controlled, 26°C	3	3	Not registered (central supply to govern-ment centres)	Yellow coloured, capsule shaped, biconvex film-coated tablets, debossed with 'H' on one side and '4' on the other side	✓	✓ 95.6	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): 111.1%	✓
RW/ EFV/ 006/ 23.nov.2015	30 tablets in plastic bottle	Hetero Labs Ltd	Polepally Village, Mahaboob Nagar, Andhra Pradesh, India	EFZ114010	8 2014	7 2017	Bugesera District Pharmacy	Pharmacy, level 2, public / Eastern	Controlled, 26°C	3	3	Not registered (central supply to govern-ment centres)	Yellow coloured, capsule shaped, biconvex film-coated tablets, debossed with 'H' on one side and '4' on the other side	✓	✓ 93.5	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): 97.1%	✓
RW/ EFV/ 007/ 23.11.2015	30 tablets in plastic bottle	Hetero Labs Ltd	Polepally Village, Mahaboob Nagar, Andhra Pradesh, India	EFZ114010	8 2014	7 2017	Nyamata District Hospital	Hospital, level 2, public / Eastern	Controlled, 26°C	3	3	Not registered (central supply to govern-ment centres)	Yellow coloured, capsule shaped, biconvex film-coated tablets, debossed with 'H' on one side and '4' on the other side	✓	✓ 95.6	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): 103.2%	✓
RW/ EFV/ 005/ 20.11.2017	30 tablets in plastic bottle	Hetero Labs Ltd	Polepally Village, Mahaboob Nagar, Andhra Pradesh, India	EFZ114010	8 2014	7 2017	Kinyinya Health Facility	Treatment centre, level 2, public / Kigali	Controlled, 24°C	3	3	Not registered (central supply to govern-ment centres)	Yellow coloured, capsule shaped, biconvex film-coated tablets, debossed with 'H' on one side and '4' on the other side	✓	✓ 95.0	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): 97.3%	✓
RW/ EFV/ 004/ 20.11.2015	30 tablets in plastic bottle	Hetero Labs Ltd	Polepally Village, Mahaboob Nagar, Andhra Pradesh, India	EFZ114010	8 2014	7 2017	Muhima District Hospital, Kigali	Hospital, level 2, public / Kigali	Controlled, 26°C	3	3	Not registered (central supply to govern-ment centres)	Yellow coloured, capsule shaped, biconvex film-coated tablets, debossed with 'H' on one side and '4' on the other side	✓	✓ 94.0	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): 101.7%	✓

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Country of collection * / sample code	Pack size	Manu–facturer	Manufacturing site	Batch number	Manu-facture date	Expiry date	Sampling site	Type of sampling site / region	Storage conditions at sampling site	Shelf life claimed (years)	PQ current approved shelf life (years)	Registra–tion status	Appearance	Iden-tity	Assay %	Uni-formity of dosage units	Dissolu-tion	Con-clu-sion
ZM/ EFV/ 003/ 021115	30 tablets in plastic bottle	Strides Arcolab Ltd	Suragajakkana-halli, Indlawadi Cross, Anekal Taluk, Bangalore, Karnataka, India	7222188	8 2014	7 2017	Siavonga District Hospital	Hospital, level 2, public / Southern	Controlled, 28°C	3	3	Registered	Yellow-off white coloured, capsule shaped, biconvex film-coated tablets, plain on both sides	✓	✓ 98.0	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): 91.0%	✓
ZM/ EFV/ 004/ 021115	30 tablets in plastic bottle	Strides Arcolab Ltd	Suragajakkana-halli, Indlawadi Cross, Anekal Taluk, Bangalore, Karnataka, India	7222277	7 2014	6 2017	Ndola Central Hospital	Hospital, level 2, public / Copperbelt	Controlled, 27.9°C, 42% RH	3	3	Registered	Yellow-off white coloured, capsule shaped, biconvex film-coated tablets, plain on both sides	✓	✓ 95.4	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): 89.9%	✓
ZM/ EFV/ 005/ 021115	30 tablets in plastic bottle	Micro Labs Ltd	Verna, Goa, India	EUAG069	8 2014	7 2016	Hilltop Hospital, Ndola	Hospital, level 2, private / Copperbelt	Not con-trolled, 33°C, 42% RH	2	n/a	Pending (supplied on special MoH per-mission)	Yellow coloured, oval shaped, biconvex film-coated tablets, debossed "O" on one side and plain on the other	✓	✓ 95.1	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): 92.5%	✓
ZM/ EFV/ 006/ 031115	30 tablets in plastic bottle	Mylan Labo-ratories Ltd	Waluj, Aurangabad, Maharashtra, India	3039279	5 2015	4 2018	Chikankata Mission Hospital	Hospital, level 2, NGO / Southern	Controlled, 25°C, 40% RH	3	3	Registered	Yellow-peach coloured, capsule shaped, biconvex film-coated tablets, debossed “M109” on one side and plain on the other	✓	✓ 93.8	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): 93.7%	✓
ZM/ EFV/ 008/ 031115	30 tablets in plastic bottle	Hetero Labs Ltd	Polepally Village, Mahaboob Nagar, Andhra Pradesh, India	EFZ115009	4 2015	3 2018	Mpongwe District Health Office, Ndola Rural	Treatment centre, level 2, public / Copperbelt	Controlled, 24°C, 40% RH	3	3	Registered	Yellow coloured, capsule shaped, biconvex film-coated tablets, debossed with ‘H’ on one side and ‘4’ on the other side	✓	✓ 92.2	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): 93.5%	✓
ZM/ EFV/ 009/ 061115	30 tablets in plastic bottle	Cipla Ltd	Verna, Goa, India	G38428	12 2013	11 2016	Prime Pharmaceuticals Ltd, Lusaka	Importer, level 1, private / Lusaka	Controlled, 22°C, 32% RH	3	3	Registered	Yellow coloured, capsule shaped, biconvex film-coated tablets, debossed ‘EFV’ on one side and plain on the other	✓	✓ 96.2	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): 93.2%	✓
ZM/ EFV/ 010/ 041115	30 tablets in plastic bottle	Micro Labs Ltd	Verna, Goa, India	EUAG069	8 2014	7 2016	Kasama General Hospital	Hospital, level 2, public / Northern	Controlled, 29°C, 32% RH	2	n/a	Pending (supplied on special MoH per-mission)	Yellow coloured, oval shaped, biconvex film-coated tablets, debossed "O" on one side and plain on the other	✓	✓ 92.4	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): 91.9%	✓

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Country of collection * / sample code	Pack size	Manu–facturer	Manufacturing site	Batch number	Manu-facture date	Expiry date	Sampling site	Type of sampling site / region	Storage conditions at sampling site	Shelf life claimed (years)	PQ current appro-ved shelf life (years)	Registra–tion status	Appearance	Iden-tity	Assay %	Uni-formity of dosage units	Dissolu-tion	Con-clu-sion
ZM/ EFV/ 014/ 031115	30 tablets in plastic bottle	Strides Arcolab Ltd	Suragajakkana-halli, Indlawadi Cross, Anekal Taluk, Bangalore, Karnataka, India	7222764	11 2014	10 2017	Livingstone General Hospital	Hospital, level 2, public / Southern	Controlled, 28°C	3	3	Registered	Yellow-off white coloured, capsule shaped, biconvex film-coated tablets, plain on both sides	✓	✓ 96.9	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): 93.0%	✓
ZM/ EFV/ 019/ 061115	30 tablets in plastic bottle	Mylan Labo-ratories Ltd	Waluj, Aurangabad, Maharashtra, India	3039287	5 2015	4 2018	Churches Health Association of Zambia, Lusaka	Importer, level 1, NGO / Lusaka	Controlled, 24°C, 32% RH	3	3	Registered	Yellow-peach coloured, capsule shaped, biconvex film-coated tablets, debossed "M109" on one side and plain on the other	✓	✓ 94.9	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): 93.2%	✓
ZM/ EFV/ 020/ 051115	30 tablets in plastic bottle	Hetero Labs Ltd	Polepally Village, Mahaboob Nagar, Andhra Pradesh, India	EFZ115009	4 2015	3 2018	Isoka District Health Office	Treatment centre, level 2, public / Muchinga	Controlled, 18°C, 34% RH	3	3	Registered	Yellow coloured, capsule shaped, biconvex film-coated tablets, debossed with 'H' on one side and '4' on the other side	✓	✓ 98.3	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): 91.2%	✓
ZM/ EFV/ 021/ 061115	30 tablets in plastic bottle	Strides Arcolab Ltd	Suragajakkana-halli, Indlawadi Cross, Anekal Taluk, Bangalore, Karnataka, India	7222277	7 2014	6 2017	Chitambo Mission Hospital	Hospital, level 2, NGO / Central	Controlled, 24°C, 32% RH	3	3	Registered	Yellow-off white coloured, capsule shaped, biconvex film-coated tablets, plain on both sides	✓	✓ 96.7	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): 88.5%	✓
ZM/ EFV/ 022/ 061115	30 tablets in plastic bottle	Mylan Labo-ratories Ltd	Waluj, Aurangabad, Maharashtra, India	3036919	3 2015	2 2018	Gwembe District Hospital	Hospital, level 2, public / Southern	Controlled, 18°C, 38% RH	3	3	Registered	Yellow-peach coloured, capsule shaped, biconvex film-coated tablets, debossed "M109" on one side and plain on the other	✓	✓ 98.9	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): 94.9%	✓

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Appendix 4 Efavirenz/emtricitabine/tenofovir disoproxil fumarate 600/200/300 mg tablets – test results

Specifications:

Assay: 90.0-110.0% for each API
Tenofovir monosoproxil-impurity: NMT 5.0%
Water content: NMT 50 mg/g
Uniformity of dosage units: according to USP ⟨905⟩ - Weight variation
Dissolution: NLT 80% (Q) in 30 minutes for each API

Country of collection * / sample code	Pack size	Manu-facturer	Manufac-turing site	Batch num-ber	Manu-fac-ture date	Ex-piry date	Sampling site	Type of sampling site / region	Storage condi-tions at sampling site	Shelf life claimed (years)	PQ current appro-ved shelf life (years)	Regis-tration status	Appearance	Iden-tity	Assay** %			Tenofo-vir mono-soproxil impu-rity %	Water con-tent mg/g	Uni-formity of dosage units**	Disso-lution **	Con-clu-sion
															EFV	EMT	TDF					
BF/ TEE/ 10/ 09112015	30 tablets in plastic bottle	Hetero Labs Ltd	Polepally Village, Mahaboob Nagar, Andhra Pradesh, India	EET11 5003	1 2015	12 2017	Centrale d'Achat des Médicaments Essentiels Génériques et des Consom-mables médicaux (CAMEG), ZAD Ouaga-dougou	Importer, level 1, public / Centre	Con-trolled, 17°C	3	3	Regis-tered	Dusky pink, oblong, film-coated tablets, debossed 'H' on one side and '128' on the other	✓	✓ 99.0	✓ 97.1	✓ 93.6	✓ 1.6	✓ 8.5	✓ EFV: AV (n=10): 1.8 EMT: AV (n=10): 3.2 TDF: AV (n=10): 6.6	✓ at S1 Ø (n=6): EFV: 93.9% EMT: 101.2% TDF 94.5%	✓
BF/ TEE/ 11/ 17112015	30 tablets in plastic bottle	Cipla Ltd	Verna, Goa, India	G4471 7	7 2014	6 2017	Centre médical avec antenne chirurgicale (CMA), Dô	Hospital, level 2, public / Hauts-Bassins	Not con-trolled, air-condi-tioned	3	3	Not registe-red (dona-tion)	Dusky pink, oblong, film-coated tablets, plain on both sides	✓	✓ 98.8	✓ 96.9	✓ 94.0	✓ 1.9	✓ 9.4	✓ EFV: AV (n=10): 1.7 EMT: AV (n=10): 2.9 TDF: AV (n=10): 5.8	✓ at S1 Ø (n=6): EFV: 96.2% EMT: 99.7% TDF: 97.9%	✓

** EFV = efavirenz, EMT = emtricitabine, TDF = tenofovir disoproxil fumarate
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✓= complies; ✖= does not comply

Country of collection * / sample code	Pack size	Manufacturer	Manufacturing site	Batch number	Manufacture date	Expiry date	Sampling site	Type of sampling site / region	Storage conditions at sampling site	Shelf life claimed (years)	PQ current approved shelf life (years)	Registration status	Appearance	Identity	Assay** %			Tenofovir monosoproxil impurity %	Water content mg/g	Uniformity of dosage units**	Dissolution **	Conclusion
															EFV	EMT	TDF					
BF/ TEE/ 12/ 09112015	30 tablets in plastic bottle	Mylan Laboratories Ltd	Waluj, Aurangabad, Maharashtra, India	8028467	6 2014	5 2017	Centrale d'Achat des Médicaments Essentiels Génériques et des Consommables médicaux (CAMEG), ZAD Ouagadougou	Importer, level 1, public / Centre	Controlled, 31.1°C, 33.3% RH	3	3	Registered	Dusky pink, oblong, film-coated tablets with imprint "M171" on one side, plain on the other	✓	✓ 99.9	✓ 95.6	✓ 93.2	✓ 1.1	✓ 7.5	✓ EFV: AV (n=10): 3.4 EMT: AV (n=10): 6.3 TDF: AV (n=10): 8.5	✓ at S2 Ø (n=12): EFV: 86.5% EMT: 98.5% TDF: 94.2%	✓
BF/ TEE/ 13/ 12112015	30 tablets in plastic bottle	Cipla Ltd	Verna, Goa, India	X40589	7 2014	6 2016	Centre hospitalier universitaire pédiatrique Charles-de-Gaulle (CHUP-CDG), Ouagadougou	Hospital, level 2, public / Centre	Not controlled, air-conditioned, 18°C	2	3	Not registered (donation)	Dusky pink, oblong, film-coated tablets with "V" debossed on one side and plain on the other	✓	✓ 99.0	✓ 97.3	✓ 95.7	✓ 2.0	✓ 9.6	✓ EFV: AV (n=10): 1.0 EMT: AV (n=10): 6.3 TDF: AV (n=10): 8.5	✓ at S1 Ø (n=6): EFV: 96.9% EMT: 98.6% TDF: 98.4%	✓
BF/ TEE/ 14/ 17112015	30 tablets in plastic bottle	Mylan Laboratories Ltd	Sinnar, Nashik, Maharashtra, India	8028126	9 2014	8 2016	Centre hôpitalier universitaire Sourou Sanou (CHUSS), Bobo-Dioulasso	Hospital, level 2, public / Hauts-Bassins	Controlled, 26.6°C	2	3	Registered	Dusky pink, oblong, film-coated tablets with imprint "M171" on one side, plain on the other	✓	✓ 100.0	✓ 98.8	✓ 95.1	✓ 1.2	✓ 8.4	✓ EFV: AV (n=10): 2.5 EMT: AV (n=10): 2.5 TDF: AV (n=10): 5.7	✓ at S1 Ø (n=6): EFV: 90.0% EMT: 98.8% TDF: 92.5%	✓

** EMT = emtricitabine, TDF = tenofovir disoproxil fumarate

* BF = Burkina Faso, DRC = Democratic Republic of the Congo, NG = Nigeria, RW = Rwanda, ZM = Zambia

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Country of collection * / sample code	Pack size	Manufacturer	Manufacturing site	Batch number	Manufacture date	Expiry date	Sampling site	Type of sampling site / region	Storage conditions at sampling site	Shelf life claimed (years)	PQ current approved shelf life (years)	Registration status	Appearance	Identity	Assay** %			Tenofovir monosoproxil impurity %	Water content mg/g	Uniformity of dosage units**	Dissolution **	Conclusion
															EFV	EMT	TDF					
BF/ TEE/ 15/ 17112015	30 tablets in plastic bottle	Hetero Labs Ltd	Polepally Village, Mahaboob Nagar, Andhra Pradesh, India	EET115004A	1 2015	12 2017	Association Responsabilité-Espoir-Vie-Solidarité (ONG REVS+), Bobo-Dioulasso	Treatment centre, level 2, private / Hauts-Bassins	Not controlled, air-conditioned	3	3	Registered	Dusky pink, oblong, film-coated tablets, debossed 'H' on one side and '128' on the other	✓	✓ 98.9	✓ 97.8	✓ 94.8	✓ 1.6	✓ 7.6	✓ EFV: AV (n=10): 4.2 EMT: AV (n=10): 4.8 TDF: AV (n=10): 7.7	✓ at S1 Ø (n=6): EFV: 96.9% EMT: 98.4% TDF: 93.2%	✓
ZM/ TEE/ 001/ 021115	30 tablets in plastic bottle	Cipla Ltd	Verna, Goa, India	X30938	10 2013	9 2016	Ndola Central Hospital	Hospital, level 2, public / Copperbelt	Controlled, 27.9°C, 42% RH	3	3	Registered	Dusky pink, oblong, film-coated tablets, plain on both sides	✓	✓ 101.0	✓ 98.0	✓ 97.1	✓ 1.0	✓ 10.8	✓ EFV: AV (n=10): 0.7 EMT: AV (n=10): 1.0 TDF: AV (n=10): 1.9	✓ at S1 Ø (n=6): EFV: 98.7% EMT: 100.5% TDF: 97.5%	✓
ZM/ TEE/ 011/ 041115	30 tablets in plastic bottle	Mylan Laboratories Ltd	Waluj, Aurangabad, Maharashtra, India	3014367	7 2013	6 2016	Kasama General Hospital	Hospital, level 2, public / Northern	Controlled, 29°C, 32% RH	3	3	Registered	Dusky pink, oblong, film-coated tablets with imprint "M171" on one side, plain on the other	✓	✓ 98.8	✓ 100.8	✓ 98.7	✓ 0.9	✓ 8.8	✓ EFV: AV (n=10): 3.7 EMT: AV (n=10): 3.8 TDF: AV (n=10): 3.7	✓ at S2 Ø (n=12): EFV: 90.9% EMT: 90.6% TDF: 85.8%	✓

** EFV = efavirenz, EMT = emtricitabine, TDF = tenofovir disoproxil fumarate

* BF = Burkina Faso, DRC = Democratic Republic of the Congo, NG = Nigeria, RW = Rwanda, ZM = Zambia

✓= complies; ✖= does not comply

Country of collection * / sample code	Pack size	Manufacturer	Manufacturing site	Batch number	Manufacture date	Expiry date	Sampling site	Type of sampling site / region	Storage conditions at sampling site	Shelf life claimed (years)	PQ current approved shelf life (years)	Registration status	Appearance	Identity	Assay** %			Tenofovir monosoproxil impurity %	Water content mg/g	Uniformity of dosage units**	Dissolution **	Conclusion
															EFV	EMT	TDF					
ZM/ TEE/ 013/ 061115	30 tablets in plastic bottle	Mylan Laboratories Ltd	Waluj, Aurangabad, Maharashtra, India	3014365	6 2013	5 2016	Medical Stores Ltd, Lusaka	Medical store, level 1, public / Lusaka	Controlled, 24°C, 32% RH	3	3	Registered	Dusky pink, oblong, film-coated tablets with imprint "M171" on one side, plain on the other	✓	✓ 96.1	✓ 102.4	✓ 100.9	✓ 0.8%	✓ 8.3	✓ EFV: AV (n=10): 6.8 EMT: AV (n=10): 5.4 TDF: AV (n=10): 4.6	✓ at S2 Ø (n=12): EFV: 86.2% EMT: 92.7% TDF: 87.7%	✓
ZM/ TEE/ 018/ 061115	30 tablets in plastic bottle	Cipla Ltd	Verna, Goa, India	G44373	3 2014	2 2017	Prime Pharmaceuticals Ltd, Lusaka	Importer, level 1, private / Lusaka	Controlled, 22°C, 32% RH	3	3	Registered	Dusky pink, oblong, film-coated tablets, plain on both sides	✓	✓ 99.0	✓ 99.3	✓ 97.1	✓ 1.4	✓ 8.1	✓ EFV: AV (n=10): 1.9 EMT: AV (n=10): 1.9 TDF: AV (n=10): 3.1	✓ at S1 Ø (n=6): EFV: 93.8% EMT: 99.8% TDF: 96.8%	✓

** EMT = emtricitabine, TDF = tenofovir disoproxil fumarate

* BF = Burkina Faso, DRC = Democratic Republic of the Congo, NG = Nigeria, RW = Rwanda, ZM = Zambia

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Appendix 5 Lamivudine 150 mg tablets – test results

Specifications:

Assay: 95.0-105.0%;
Uniformity of dosage units: **A:** according to Ph. Int. 5.2 - Uniformity of mass, **B:** according to USP ⟨905⟩ - Weight variation
Dissolution: NLT 75%(Q) in 45 minutes

Country of collection* / sample code	Pack size	Manu-facturer	Manu-facturing site	Batch number	Manu-factur e date	Ex-piry date	Sampling site	Type of sampling site / region	Storage condi-tions at sampling site	Shelf life clai-med (years)	PQ current appro-ved shelf life (years)	Regis-tration status	Appearance	Iden-tity	Assay %	Uniformity of dosage units	Dissolution	Con-clu-sion
BF/ LAT/ 01/ 09112015	60 tablets in plastic bottle	Auro-bindo Pharma Ltd	Bachupally Village, Ranga Reddy, Telangana, India	LV1514 026-B	11 2014	10 2017	Centrale d'Achat des Médicaments Essentiels Génériques et des Consommables médicaux (CAMEG), ZAD Ouagadougou	Importer, level 1, public / Centre	Con-trolled, 17°C	3	n/a	Not registe-red (dona-tion)	White film-coated oblong tablets, debossed "63" on one side and "C" on the other	✓	✓ 98.3	✓ A. Ø (n=20): 287.6mg, max dev: -2.5%; B. AV (n=10): 2.5	✓ at S1 Ø (n=6): 99.3%	✓t
BF/ LAT/ 02/ 11112015	60 tablets in plastic bottle	Mac-leods Pharma-ceuticals Ltd	Kachigam, Daman, India	ELC940 8B	9 2014	8 2016	Centre hospitalier universitaire pédiatrique Charles-de-Gaulle (CHUP-CDG), Ouagadougou	Hospital, level 2, public / Centre	Not con-trolled, air-condi-tioned, 18°C	2	3	Not registe-red (dona-tion)	White, bevel edged, biconvex, uncoated oblong shaped tablets, debossed "ML 1" on one side, scored on the other	✓	✓ 98.1	✓ A. Ø (n=20): 312.6mg, max dev: +1.8%; B. AV (n=10): 2.2	✓ at S1 Ø (n=6): 98.6%	✓
BF/ LAT/ 03/ 16112015	60 tablets in plastic bottle	Mac-leods Pharma-ceuticals Ltd	Kachigam, Daman, India	ELC940 9A	12 2014	11 2016	Centre médical avec antenne chirurgicale (CMA), Dô	Hospital, level 2, public / Hauts-Bassins	Not con-trolled, air-condi-tioned	2	3	Not registe-red (dona-tion)	White, bevel edged, biconvex, uncoated oblong shaped tablets, debossed "ML 1" on one side, scored on the other Tablets in one of two collected containers contaminated with the black drying agent from burst sachet	✓	✓ 98.1	✓ A. Ø (n=20): 310.4mg, max dev: -1.4%; B. AV (n=10): 1.8	✓ at S1 Ø (n=6): 97.9%	✖

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✓= complies; ✖= does not comply

Country of collection* / sample code	Pack size	Manu-facturer	Manu-facturing site	Batch number	Manu-factur e date	Ex-piry date	Sampling site	Type of sampling site / region	Storage condi-tions at sampling site	Shelf life clai-med (years)	PQ current appro-ved shelf life (years)	Regis-tration status	Appearance	Iden-tity	Assay %	Uniformity of dosage units	Dissolution	Con-clu-sion
DRC/ LAT/ 06/ 27-10-15	60 tablets in plastic bottle	Cipla Ltd	Meditab Specialties Pvt Ltd, Kundaim, Goa, India	KG50644	7 2015	6 2018	Bolloré Transport & Logistics, Bobozo, Kinshasa	Medical store, level 1, private / Kinshasa	Con-trolled, 21°C, 56% RH	3	3	Not registe-red (supplied on special permis-sion)	White film-coated capsule shaped, biconvex tablets, debossed "LVR" on one side, central break line on the other	✓	✖ BP method: 93.3 ✓ Manu-facturer's method: 96.1	✓ A. Ø (n=20): 297.5 mg, max dev: -3.8%; B. AV (n=10): 9.5	✓ at S1 Ø (n=6): 100.0%	✓
DRC/ LAT 8/ 27-10-15	60 tablets in plastic bottle	Micro Labs Ltd	Verna, Goa, India	LXAG031	10 2014	9 2016	Centrale d'Achat des Médicaments Essentiels de Kinshasa (CAMESKIN), Kinshasa	Medical store, level 1, NGO / Kinshasa	Con-trolled, 29.5°C, 51% RH	2	4	Not registe-red (supplied on special permis-sion)	White, circular binconvex, film-coated tablets, debossed "108" on one side, scored on the other	✓	✓ 98.1	✓ A. Ø (n=20): 286.4mg, max dev: +1.4%; B. AV (n=10): 2.2	✓ at S1 Ø (n=6): 101.6%	✓
DRC/ LAT/ 09/ 10-11-15	60 tablets in plastic bottle	Micro Labs Ltd	Verna, Goa, India	LXAG031	10 2014	9 2016	Centrale d'Achat des Médicaments Essentiels de Lubumbashi (CAMELU), Katanga	Medical store, level 1, NGO / Haut-Katanga	Con-trolled, 24°C, 52% RH	2	4	Not registe-red (supplied on special permis-sion)	White, circular binconvex, film-coated tablets, debossed "108" on one side, scored on the other	✓	✓ 97.9	✓ A. Ø (n=20): 288.4mg, max dev: +1.4%; B. AV (n=10): 2.2	✓ at S1 Ø (n=6): 101.4%	✓
ZM/ LAT/ 007/ 051115	60 tablets in plastic bottle	Hetero Labs Ltd	Jeedimetla, Hyderabad, Andhra Pradesh, India	E141585	9 2014	8 2016	Isoka District Health Office	Treatme nt centre, level 2, public / Muchinga	Con-trolled, 18°C, 34% RH	2	3	Registe red	White film-coated oval tablets, debossed "3" and "0" on either side of the score line on one side and "H" on the other	✓	✓ 96.9	✓ A. Ø (n=20): 283.9mg, max dev: +4.6%; B. AV (n=10): 7.2	✓ at S1 Ø (n=6): 100.5%	✓
ZM/ LAT/ 012/ 061115	60 tablets in plastic bottle	Auro-bindo Pharma Ltd	Bachupally Village, Ranga Reddy, Telangana, India	LV1513033-A	12 2013	11 2016	Churches Health Association of Zambia, Lusaka	Importer, level 1, NGO / Lusaka	Con-trolled, 24°C, 32% RH	3	n/a	Registe red	White film-coated oblong tablets, debossed "63" on one side and "C" on the other	✓	✓ 97.3	✓ A. Ø (n=20): 285.7mg, max dev: +2.4%; B. AV (n=10): 3.5	✓ at S1 Ø (n=6): 100.5%	✓

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✓= complies; ✖= does not comply

Country of collection* / sample code	Pack size	Manu-facturer	Manu-facturing site	Batch number	Manu-facture date	Ex-piry date	Sampling site	Type of sampling site / region	Storage condi-tions at sampling site	Shelf life clai-med (years)	PQ current appro-ved shelf life (years)	Regis-tration status	Appearance	Iden-tity	Assay %	Uniformity of dosage units	Dissolution	Con-clu-sion
ZM/ LAT/ 015/ 061115	60 tablets in plastic bottle	Hetero Labs Ltd	Jeedimetla, Hyderabad, Andhra Pradesh, India	E141585	9 2014	8 2016	University Teaching Hospital, Lusaka	Hospital, level 1, public / Lusaka	Con-trolled, 21.5°C, 32% RH	2	3	Registered	White film-coated oval tablets, debossed "3" and "0" on either side of the score line on one side and "H" on the other	✓	✓ 96.5	✓ A. Ø (n=20): 281.8mg, max dev: +2.4%; B. AV (n=10): 4.3	✓ at S1 Ø (n=6): 98.7%	✓
ZM/ LAT/ 016/ 031115	60 tablets in plastic bottle	Auro-bindo Pharma Ltd	Bachupally Village, Ranga Reddy, Telangana, India	LV1513 025-A	8 2013	7 2016	Livingstone General Hospital	Hospital, level 2, public / Southern	Con-trolled, 28°C, 36% RH	3	n/a	Registered	White film-coated oblong tablets, debossed "63" on one side and "C" on the other	✓	✓ 97.6	✓ A. Ø (n=20): 285.2mg, max dev: -3.1%; B. AV (n=10): 3.6	✓ at S1 Ø (n=6): 99.6%	✓
ZM/ LAT/ 017/ 031115	60 tablets in plastic bottle	Auro-bindo Pharma Ltd	Bachupally Village, Ranga Reddy, Telangana, India	LV1513 033-A	12 2013	11 2016	Chikankata Mission Hospital	Hospital, level 2, NGO / Southern	Con-trolled, 25°C, 34% RH	3	n/a	Registered	White film-coated oblong tablets, debossed "63" on one side and "C" on the other	✓	✓ 97.6	✓ A. Ø (n=20): 285.5 mg, max dev: +1.4%; B. AV (n=10): 2.5	✓ at S1 Ø (n=6): 99.9%	✓

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✓= complies; ✖= does not comply

Appendix 6 Lamivudine/nevirapine/zidovudine tablets – test results

Specifications:

Assay: 90.0-110.0% for each API
Uniformity of dosage units: according to USP ⟨905⟩ - Weight variation
Dissolution of nevirapine: NLT 75% (Q) in 60 minutes
Related substances, Ph.Int.: zidovudine impurity C (thymine) NMT 2%; zidovudine impurity B NMT 1%; nevirapine impurity B NMT 0.2%
any peak eluting after nevirapine NMT 0.2%; any peak eluting before lamivudine NMT 0.3%
Related substances, manufacturer's specification: zidovudine impurity C (thymine) NMT 2%; any unknown impurity NMT 0.2%; total impurities NMT 3.5%

Lamivudine/nevirapine/zidovudine 30/50/60 mg dispersible tablets

Country of collection*/ sample code	Pack size	Manufacturer	Manufacturing site	Batch number	Manufacture date	Expiry date	Sampling site	Type of sampling site / region	Storage conditions at sampling site	Shelf life claimed (years)	PQ current approved shelf life (years)	Registration status	Appearance	Identity	Assay %			Related substances	Uniformity of dosage units	Dissolution of nevirapine	Disintegration	Fineness of dispersion	Conclusion
															Lamivudine	Nevirapine	Zidovudine						
BF/ LNZ/ 09/ 09112015	60 tablets in plastic bottle	Mylan Laboratories Ltd	Indore, Pithampur, Madhya Pradesh, India	3031579	10 2014	9 2019	Centrale d'Achat des Médicaments Essentiels Génériques et des Consommables médicaux (CAMEG), ZAD Ouagadougou	Importer, level 1, public / Centre	Controlled, 17°C	5	5	Registered	Round, yellowish tablets, scored on one side with "M09" debossed on one side of the score line, and plain on the other side of the tablet	✓	✓ 99.3	✓ 99.8	✓ 101.9	✓ zid.imp.C: <LOD zid.imp.B: <LOD nev.imp.B: <LOD peak after nev.: <LOD peak before lam.: max 0.2%	✓ lam.: AV (n=10): 2.6 nev.: AV (n=10): 2.7 zid.: AV (n=10): 3.1	✓ at S1 Ø (n=6): 100.2%	✓	✓	✓

**zid.=zidovudine; nev.=nevirapine, lam.=lamivudine; imp.=impurity
* BF = Burkina Faso, DRC = Democratic Republic of the Congo, NG = Nigeria, RW = Rwanda, ZM = Zambia

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Country of collection*/ sample code	Pack size	Manufacturer	Manufacturing site	Batch number	Manufacture date	Expiry date	Sampling site	Type of sampling site / region	Storage conditions at sampling site	Shelf life claimed (years)	PQ current approved shelf life (years)	Registration status	Appearance	Identity	Assay %			Related substances	Uniformity of dosage units	Dissolution of nevirapine	Disintegration	Fineness of dispersion	Conclusion
															Lamivudine	Nevirapine	Zidovudine						
BF/ LNZ/ 08/ 23112015	60 tablets in plastic bottle	Mylan Laboratories Ltd	Indore, Pithampur, Madhya Pradesh, India	3031579	10 2014	9 2019	Association vie positive, Ouagadougou	Treatment centre, level 2, private / Centre	Not controlled, 32°C	5	5	Registered	Round, yellowish tablets, scored on one side with "M09" debossed on one side of the score line, and plain on the other side of the tablet	✓	✓ 97.4	✓ 100.0	✓ 98.3	✓ zid.imp.C: <LOD zid.imp.B: <LOD nev.imp.B: <LOD peak after nev.: <LOD peak before lam.: max 0.2%	✓ lam.: AV (n=10): 5.0 nev.: AV (n=10): 4.0 zid.: AV (n=10): 4.1	✓ at S1 Ø (n=6): 97.5%	✓	✓	✓
DRC/ LNZ/ 02/ 27-10-15	60 tablets in plastic bottle	Mylan Laboratories Ltd	Waluj, Aurangabad, Maharashtra, India	3024282	3 2014	2 2019	Bolloré Transport & Logistics, Bobozo, Kinshasa	Medical store, level 1, private / Kinshasa	Controlled, 21°C, 56% RH	5	5	Not registered (supplied on special permission)	Round, yellowish tablets, scored on one side with "M09" debossed on one side of the score line, and plain on the other side of the tablet	✓	✓ 100.1	✓ 97.4	✓ 98.8	✓ zid.imp.C: <LOD zid.imp.B: 0.1% nev.imp.B: <LOD peak after nev.: max 0.03% peak before lam.: max 0.1%	✓ lam.: AV (n=10): 2.1 nev. AV (n=10): 3.1 zid.: AV (n=10): 2.0	✓ at S1 Ø (n=6): 99.5%	✓	✓	✓
DRC/ LNZ/ 10/ 10-11-15	60 tablets in plastic bottle	Mylan Laboratories Ltd	Sinnar, Nashik, Maharashtra, India	3029476	8 2014	7 2016	Centrale d'Achat des Médicaments Essentiels de Lubumbashi (CAMELU), Katanga	Medical store, level 1, NGO / Haut-Katanga	Controlled, 21°C, 52% RH	2	5	Not registered (supplied on special permission)	Round, yellowish tablets, scored on one side with "M09" debossed on one side of the score line, and plain on the other side of the tablet	✓	✓ 101.6	✓ 96.3	✓ 99.2	✓ zid.imp.C: <LOD zid.imp.B: 0.1% nev.imp.B: <LOD peak after nev.: max 0.03% peak before lam.: max 0.1%	✓ lam.: AV (n=10): 3.0 nev.: AV (n=10): 4.9 ZID.: AV (n=10): 2.8	✓ at S1 Ø (n=6): 100.2%	✓	✓	✓

**zid.=zidovudine; nev.=nevirapine, lam.=lamivudine; imp.=impurity

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✓= complies; ✖= does not comply

Country of collection*/ sample code	Pack size	Manufacturer	Manufacturing site	Batch number	Manufacture date	Expiry date	Sampling site	Type of sampling site / region	Storage conditions at sampling site	Shelf life claimed (years)	PQ current approved shelf life (years)	Registration status	Appearance	Identity	Assay %			Related substances	Uniformity of dosage units	Dissolution of nevirapine	Disintegration	Fineness of dispersion	Conclusion
															Lamivudine	Nevirapine	Zidovudine						
DRC/ LNZ/ 13/ 05-11-15	60 tablets in plastic bottle	Mylan Laboratories Ltd	Waluj, Aurangabad, Maharashtra, India	3024281	3 2014	2 2019	Centrale d'Achat et d'Approvisionnement en Médicaments Essentiels du Bas Congo Ouest (CAAMEBO), Matadi	Medical store, level 2, NGO / Kongo Central	Controlled, 27°C, 63% RH	5	5	Not registered (supplied on special permission)	Round, yellowish tablets, scored on one side with "M09" debossed on one side of the score line, and plain on the other side of the tablet	✓	✓ 101.1	✓ 98.3	✓ 100.4	✓ zid.imp.C: <LOD zid.imp.B: 0.1% nev.imp.B: <LOD peak after nev.: max 0.04% peak before lam.: max 0.1%	✓ lam.: AV (n=10): 2.4 nev.: AV (n=10): 2.3 zid.: AV (n=10): 2.4	✓ at S1 Ø (n=6): 101.5%	✓	✓	✓
DRC/ LNZ/ 26/ 10-11-15	60 tablets in plastic bottle	Mylan Laboratories Ltd	Waluj, Aurangabad, Maharashtra, India	3013726	6 2013	5 2017	Centrale d'Achat des Médicaments Essentiels de Kisangani (CAMEKIS), Kisangani	Medical store, level 2, NGO / Tshopo	Controlled, 25.3°C, 53% RH	4	5	Not registered (supplied on special permission)	Round, yellowish tablets, scored on one side with "M09" debossed on one side of the score line, and plain on the other side of the tablet	✓	✓ 97.1	✓ 96.9	✓ 97.8	✖ zid.imp.C: <LOD zid.imp.B: 0.04% nev.imp.B: 0.04% peak after nev.: max 0.6% peak before lam.: max 0.1%) ✓ retest by manufacturer's method: zid.imp.C: <LOD any unknown imp.: max 0.1% sum: 0.2%	✓ lam.: AV (n=10): 3.0 nev.: AV (n=10): 3.2 zid.: AV (n=10): 2.4	✓ at S1 Ø (n=6): 99.3%	✓	✓	✓

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Country of collection*/ sample code	Pack size	Manufacturer	Manufacturing site	Batch number	Manufacture date	Expiry date	Sampling site	Type of sampling site / region	Storage conditions at sampling site	Shelf life claimed (years)	PQ current approved shelf life (years)	Registration status	Appearance	Identity	Assay %			Related substances	Uniformity of dosage units	Dissolution of nevirapine	Disintegration	Fineness of dispersion	Conclusion
															Lamivudine	Nevirapine	Zidovudine						
NG/ LNZ/ 03/ 090915	60 tablets in plastic bottle	Mylan Laboratories Ltd	Waluj, Aurangabad, Maharashtra, India	3034471	12 2014	11 2019	Federal Medical Stores, Oshodi, Lagos State (Govt)	Medical store, level 1, public / Lagos	Controlled, 21°C, 52% RH	5	5	Registered	Round, yellowish tablets, scored on one side with "M09" debossed on one side of the score line, and plain on the other side of the tablet	✓	✓ 98.0	✓ 96.4	✓ 101.2	✓ zid.imp.C: 0.26% zid.imp.B: 0.10% nev.imp.B: <LOD peak after nev.: <LOD peak before lam.: max 0.14%)	✓ lam.: AV (n=10): 2.3 nev.: AV (n=10): 3.9 zid.: AV (n=10): 1.9	✓ at S1 Ø (n=6): 94.2%	✓	✓	✓
NG/ LNZ/ 07/ 020915	60 tablets in plastic bottle	Strides Arcolab Ltd	Suragajakkanahalli, Indlawadi Cross, Anekal Taluk, Bangalore, Karnataka, India	7222706	11 2014	10 2016	Rural Health Hospital, Zonkwa, Kaduna State	Hospital, level 2, public / Kaduna	Controlled, 23°C, 52% RH	2	2	Registered	Round, white, biconvex tablets, debossed "LNZ" on one side and breakline on the other	✓	✓ 97.0	✓ 97.2	✓ 99.0	zid.imp.C: <LOD zid.imp.B: 0.10% nev.imp.B: <LOD peak after nev.: max 0.08% peak before lam.: max 0.08%	✓ lam.: AV (n=10): 3.3 nev.: AV (n=10): 3.0 zid.: AV (n=10): 1.8	✓ at S1 Ø (n=6): 97.7%	✓	✓	✓
NG/ LNZ/ 12/ 100915	60 tablets in plastic bottle	Mylan Laboratories Ltd	Waluj, Aurangabad, Maharashtra, India	3034471	12 2014	11 2019	Lagoon Hospital, Ikeja, Lagos State	Hospital, level 2, private / Lagos	Controlled, 21°C, 53% RH	5	5	Registered	Round, yellowish tablets, scored on one side with "M09" debossed on one side of the score line, and plain on the other side of the tablet	✓	✓ 98.6	✓ 97.1	✓ 100.5	✓ zid.imp.C: 0.26% zid.imp.B: 0.10% nev.imp.B: 0.04% peak after nev.: <LOD peak before lam.: max 0.14%	✓ lam.: AV (n=10): 1.9 nev.: AV (n=10): 3.2 zid.: AV (n=10): 1.9	✓ at S1 Ø (n=6): 94.7%	✓	✓	✓

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Country of collection*/ sample code	Pack size	Manufacturer	Manufacturing site	Batch number	Manufacture date	Expiry date	Sampling site	Type of sampling site / region	Storage conditions at sampling site	Shelf life claimed (years)	PQ current approved shelf life (years)	Registration status	Appearance	Identity	Assay %			Related substances	Uniformity of dosage units	Dissolution of nevirapine	Disintegration	Fineness of dispersion	Conclusion
															Lamivudine	Nevirapine	Zidovudine						
NG/ LNZ/ 19/ 090915	60 tablets in plastic bottle	Strides Arcolab Ltd	Suragajakkanahalli, Indlawadi Cross, Anekal Taluk, Bangalore, Karnataka, India	7223088	11 2014	10 2016	Federal Medical Stores, Oshodi, Lagos State (Govt)	Medical store, level 1, public / Lagos	Controlled, 21°C, 52% RH	2	2	Registered	Round, white, biconvex tablets, debossed "LNZ" on one side and breakline on the other	✓	✓ 96.5	✓ 96.5	✓ 98.7	zid.imp.C: <LOD zid.imp.B: 0.10% nev.imp.B: <LOD peak after nev.: 0.10% peak before lam.: max 0.08%	✓ lam.: AV (n=10): 3.5 nev.: AV (n=10): 3.5 zid.: AV (n=10): 1.5	✓ at S1 Ø (n=6): 96.7%	✓	✓	✓
NG/ LNZ/ 20/ 030915	60 tablets in plastic bottle	Mylan Laboratories Ltd	Waluj, Aurangabad, Maharashtra, India	3024285	3 2014	2 2019	General Hospital, Ikara, Kaduna State	Hospital, level 2, public / Kaduna	Controlled, 20°C, 51% RH	5	5	Registered	Round, yellowish tablets, scored on one side with "M09" debossed on one side of the score line, and plain on the other side of the tablet	✓	✓ 99.9	✓ 97.7	✓ 100.9	zid.imp.C: 0.27% zid.imp.B: 0.10% nev.imp.B: <LOD peak after nev.: 0.19% peak before lam.: max 0.10%	✓ lam: AV (n=10): 3.6 nev: AV (n=10): 4.3 zid: AV (n=10): 3.6	✓ at S1 Ø (n=6): 93.5%	✓	✓	✓
RW/ LNZ/ 002/ 18.nov.2015	60 tablets in plastic bottle	Cipla Ltd	Verna, Goa, India	X40743	9 2014	8 2016	Rwamagana Hospital, Rwamagana	Hospital, level 2, public / Eastern	Controlled, 25°C	2	n/a	Not registered (central supply to government centres)	Round, white tablets, debossed "DN" on one side and breakline on the other	✓	✓ 99.9	✓ 98.7	✓ 99.4	✓ zid.imp.C: <LOD zid.imp.B: 0.1% nev.imp.B: 0.01% peak after nev.: <LOD peak before lam.: max 0.1%	✓ lam: AV (n=10): 1.8 nev: AV (n=10): 1.8 zid: AV (n=10): 1.8	✓ at S1 Ø (n=6): 99.8%	✓	✓	✓

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* BF = Burkina Faso, DRC = Democratic Republic of the Congo, NG = Nigeria, RW = Rwanda, ZM = Zambia

✓= complies; ✖= does not comply

Country of collection*/ sample code	Pack size	Manufacturer	Manufacturing site	Batch number	Manufacture date	Expiry date	Sampling site	Type of sampling site / region	Storage conditions at sampling site	Shelf life claimed (years)	PQ current approved shelf life (years)	Registration status	Appearance	Identity	Assay %			Related substances	Uniformity of dosage units	Dissolution of nevirapine	Disintegration	Fineness of dispersion	Conclusion
															Lamivudine	Nevirapine	Zidovudine						
RW/ LNZ/ 003/ 20.nov.2015	60 tablets in plastic bottle	Mylan Laboratories Ltd	Sinnar, Nashik, Maharashtra, India	3029476	8 2014	7 2016	Medical Procurement and Production Division (MPPD), Kigali	Medical store, level 1, public / Kigali	Controlled	2	5	Not registered (central supply to government centres)	Round, yellowish tablets, scored on one side with "M09" debossed on one side of the score line, and plain on the other side of the tablet	✓	✓ 102.8	✓ 99.9	✓ 102.2	zid.imp.C: <LOD zid.imp.B: <LOD nev.imp.B: <LOD peak after nev.: <LOD peak before lam.: max 0.2%	✓ lam: AV (n=10): 3.1 nev: AV (n=10): 1.8 zid: AV (n=10): 2.5	✓ at S1 Ø (n=6): 98.8%	✓	✓	✓
RW/ LNZ/ 001/ 18.nov.2015	60 tablets in plastic bottle	Mylan Laboratories Ltd	Sinnar, Nashik, Maharashtra, India	3029476	8 2014	7 2016	Kayonza District Pharmacy	Pharmacy, level 2, public / Eastern	Controlled, 26°C	2	5	Not registered (central supply to government centres)	Round, yellowish tablets, scored on one side with "M09" debossed on one side of the score line, and plain on the other side of the tablet	✓	✓ 102.6	✓ 99.7	✓ 101.1	✓ zid.imp.C: <LOD zid.imp.B: <LOD nev.imp.B: <LOD peak after nev.: <LOD peak before lam.: max 0.1%	✓ lam: AV (n=10): 3.5 nev: AV (n=10): 2.3 zid: AV (n=10): 2.3	✓ at S1 Ø (n=6): 98.3%	✓	✓	✓
RW/ LNZ/ 005/ 20.11.2015	60 tablets in plastic bottle	Mylan Laboratories Ltd	Sinnar, Nashik, Maharashtra, India	3029476	8 2014	7 2016	Kinyinya Health Facility	Treatment centre, level 2, public / Kigali	Controlled, 24°C	2	5	Not registered (central supply to government centres)	Round, yellowish tablets, scored on one side with "M09" debossed on one side of the score line, and plain on the other side of the tablet	✓	✓ 103.2	✓ 99.0	✓ 102.9	✓ zid.imp.C: <LOD zid.imp.B: <LOD nev.imp.B: <LOD peak after nev.: <LOD peak before lam.: max 0.1%	✓ lam: AV (n=10): 3.5 nev: AV (n=10): 1.7 zid: AV (n=10): 3.2	✓ at S1 Ø (n=6): 98.0%	✓	✓	✓

**zid.=zidovudine; nev.=nevirapine, lam.=lamivudine; imp.=impurity

* BF = Burkina Faso, DRC = Democratic Republic of the Congo, NG = Nigeria, RW = Rwanda, ZM = Zambia

✓= complies; ✖= does not comply

Country of collection*/ sample code	Pack size	Manufacturer	Manufacturing site	Batch number	Manufacture date	Expiry date	Sampling site	Type of sampling site / region	Storage conditions at sampling site	Shelf life claimed (years)	PQ current approved shelf life (years)	Registration status	Appearance	Identity	Assay %			Related substances	Uniformity of dosage units	Dissolution of nevirapine	Disintegration	Fineness of dispersion	Conclusion
															Lamivudine	Nevirapine	Zidovudine						
RW/ LNZ/ 004/ 20.nov.2015	60 tablets in plastic bottle	Cipla Ltd	Verna, Goa, India	X40554	7 2014	6 2016	Muhima District Hospital, Kigali	Hospital, level 2, public / Kigali	Controlled, 26°C	2	n/a	Not registered (central supply to government centres)	Round, white tablets, debossed "DN" on one side and breakline on the other	✓	✓ 100.4	✓ 100.4	✓ 101.2	zid.imp.C: <LOD zid.imp.B: 0.1% nev.imp.B: 0.01% peak after nev.: <LOD peak before lam.: max 0.1%	✓ lam: AV (n=10): 1.5 nev: AV (n=10): 1.5 zid: AV (n=10): 1.5	✓ at S1 Ø (n=6): 100.2%	✓	✓	✓

Lamivudine/nevirapine/zidovudine 150/200/300 mg tablets

Country of collection* / sample code	Strength + dosage form	Pack size	Manufacturer	Manufacturing site	Batch number	Manufacture date	Expiry date	Sampling site	Type of sampling site / region	Storage conditions at sampling site	Shelf life claimed (years)	PQ current approved shelf life (years)	Registration status	Appearance	Identity	Assay %			Uniformity of dosage units	Dissolution of nevirapine	Conclusion
																Lamivudine	Nevirapine	Zidovudine			
DRC/ LNZ /21/06-11-15	150/200/300 mg | tab	60 tablets in plastic bottle	Mylan Laboratories Ltd	Waluj, Aurangabad, Maharashtra, India	3019016	10 2013	9 2018	Bureau Diocésain des Oeuvres Médicales (BDOM), Bukavu	Medical store, level 2, NGO / South Kivu	Controlled, 22°C, 60% RH	5	5	Not registered (supplied on special permission)	Blue, oblong tablets, debossed "M104" on one side and plain on the other	✓	✓ 101.6	✓ 96.8	✓ 97.8	✓ lam: AV (n=10): 2.6 nev: AV (n=10): 4.0 zid: AV (n=10): 3.1	✓ at S1 Ø (n=6): 100.5%	✓

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Appendix 7 Lamivudine/zidovudine tablets – test results

Specifications:

Assay: 95.0-105.0% for each API
Uniformity of dosage units: according to Ph. Int. 5.2 - Uniformity of mass
Dissolution: NLT 75%(Q) in 45 minutes for each API

Lamivudine/zidovudine 30/60 mg dispersible tablets

Country of collection* / sample code	Pack size	Manufacturer	Manufacturing site	Batch number	Manufacture date	Expiry date	Sampling site	Type of sampling site / region	Storage conditions at sampling site	Shelf life claimed (years)	PQ current approved shelf life (years)	Registration status	Appearance	Identity	Assay %		Uniformity of dosage units	Dissolution	Disintegration	Fineness of dispersion	Conclusion
															Lamivudine	Zidovudine					
BF/ LZT/ 16/ 17112015	60 tablets in plastic bottle	Cipla Ltd	Verna, Goa, India	X40647	7 2014	6 2016	Association Responsabilité-Espoir-Vie-Solidarité (ONG REVS+), Bobo-Dioulasso	Treatment centre, level 2, private / Hauts-Bassins	Not controlled, air-conditioned	2	n/a	Not registered (donation)	White to off-white round tablets, debossed "DR" on one side and breakline on the other	✓	✓ 95.1	✓ 98.8	✓ No tablet deviated by >±7.5%	✓ at S1 Ø (n=6): lam: 97.5% zid: 98.9%	✓	✓	✓
BF/ LZT/ 18/ 16112015	60 tablets in plastic bottle	Cipla Ltd	Verna, Goa, India	X40648	7 2014	6 2016	Centre médical avec antenne chirurgicale (CMA), Bogodogo	Hospital, level 2, public / Centre	Not controlled, 39°C	2	n/a	Not registered (donation)	White to off-white round tablets, debossed "DR" on one side and breakline on the other	✓	✓ 96.0	✓ 101.6	✓ No tablet deviated by >±7.5%	✓ at S1 Ø (n=6): lam: 98.4% zid: 100.1%	✓	✓	✓
BF/ LZT/ 19/ 17112015	60 tablets in plastic bottle	Cipla Ltd	Verna, Goa, India	X40893	8 2014	7 2016	Centre médical avec antenne chirurgicale (CMA), Dô	Hospital, level 2, public / Hauts-Bassins	Not controlled, air-conditioned	2	n/a	Not registered (donation)	White to off-white round tablets, debossed "DR" on one side and breakline on the other	✓	✓ 96.4	✓ 100.7	✓ No tablet deviated by >±7.5%	✓ at S1 Ø (n=6): lam: 98.7% zid: 100.1%	✓	✓	✓

**zid.=zidovudine; nev.=nevirapine, lam.=lamivudine; imp.=impurity
* BF = Burkina Faso, DRC = Democratic Republic of the Congo, NG = Nigeria, RW = Rwanda, ZM = Zambia

✓= complies; ✖= does not comply

Country of collection* / sample code	Pack size	Manufacturer	Manufacturing site	Batch number	Manufacture date	Expiry date	Sampling site	Type of sampling site / region	Storage conditions at sampling site	Shelf life claimed (years)	PQ current approved shelf life (years)	Registration status	Appearance	Identity	Assay %		Uniformity of dosage units	Dissolution	Disintegration	Fineness of dispersion	Conclusion
															Lamivudine	Zidovudine					
BF/ LZT/ 20/ 10112015	60 tablets in plastic bottle	Cipla Ltd	Verna, Goa, India	X40876	10 2014	9 2016	Centrale d'Achat des Médicaments Essentiels Génériques et des Consommables médicaux (CAMEG), ZAD Ouagadougou	Importer, level 1, public / Centre	Controlled, 31.1°C, 33.3% RH	2	n/a	Not registered (donation)	White to off-white round tablets, debossed "DR" on one side and breakline on the other	✓	✓ 95.2	✓ 99.4	✓ No tablet deviated by >±7.5%	✓ at S1 Ø (n=6): lam: 98.5% zid: 100.0%	✓	✓	✓
DRC/ LZT/ 20/ 5-11-15	60 tablets in plastic bottle	Mylan Laboratories Ltd	Waluj, Aurangabad, Maharashtra, India	3042721	8 2015	7 2017	Association Régionale d'Approvisionnement en Médicaments Essentiels (ASRAMES), Goma	Medical store, level 1, NGO / North Kivu	Controlled, 23.4°C, 59% RH	2	2	Not registered (supplied on special permission)	White, round shaped tablets, debossed "M" on one side of the tablet and score line on the other side, with "LZ" debossed to the left and "1" to the right of the score line	✓	✓ 96.8	✓ 99.7	✓ No tablet deviated by >±7.5%	✓ at S1 Ø (n=6): lam: 98.6% zid: 100.5%	✓	✓	✓
DRC/ LZT/ 03/ 27-10-15	60 tablets in plastic bottle	Mylan Laboratories Ltd	Waluj, Aurangabad, Maharashtra, India	3042841	8 2015	7 2017	Bolloré Transport & Logistics, Bobozo, Kinshasa	Medical store, level 1, private / Kinshasa	Controlled, 21°C, 56% RH	2	2	Not registered (supplied on special permission)	White, round shaped tablets, debossed "M" on one side of the tablet and score line on the other side, with "LZ" debossed to the left and "1" to the right of the score line	✓	✓ 97.5	✓ 99.0	✓ No tablet deviated by >±7.5%	✓ at S1 Ø (n=6): lam: 101.1% zid: 103.0%	✓	✓	✓
RW/ LZT/ 002/ 18.nov.2015	60 tablets in plastic bottle	Mylan Laboratories Ltd	Waluj, Aurangabad, Maharashtra, India	3031904	10 2014	9 2016	Rwamagana Hospital, Rwamagana	Hospital, level 2, public / Eastern	Controlled, 25°C	2	2	Not registered (central supply to government centres)	White, round shaped tablets, debossed "M" on one side of the tablet and score line on the other side, with "LZ" debossed to the left and "1" to the right of the score line	✓	✓ 96.5	✓ 102.8	✓ No tablet deviated by >±7.5%	✓ at S1 Ø (n=6): lam: 98.6% zid: 102.6%	✓	✓	✓

**zid.=zidovudine; nev.=nevirapine, lam.=lamivudine; imp.=impurity

* BF = Burkina Faso, DRC = Democratic Republic of the Congo, NG = Nigeria, RW = Rwanda, ZM = Zambia

✓= complies; ✖= does not comply

Country of collection* / sample code	Pack size	Manufacturer	Manufacturing site	Batch number	Manufacture date	Expiry date	Sampling site	Type of sampling site / region	Storage conditions at sampling site	Shelf life claimed (years)	PQ current approved shelf life (years)	Registration status	Appearance	Identity	Assay %		Uniformity of dosage units	Dissolution	Disintegration	Fineness of dispersion	Conclusion
															Lamivudine	Zidovudine					
RW/ LZT/ 003/ 20.nov.2015	60 tablets in plastic bottle	Mylan Laboratories Ltd	Waluj, Aurangabad, Maharashtra, India	3031904	10 2014	9 2016	Medical Procurement and Production Division (MPPD), Kigali	Medical store, level 1, public / Kigali	Controlled, 25°C	2	2	Not registered (central supply to government centres)	White, round shaped tablets, debossed "M" on one side of the tablet and score line on the other side, with "LZ" debossed to the left and "1" to the right of the score line	✓	✓ 97.3	✓ 100.4	✓ No tablet deviated by >±7.5%	✓ at S1 Ø (n=6): lam: 100.5% zid: 102.5%	✓	✓	✓
RW/ LZT/ 001/ 18.nov.2015	60 tablets in plastic bottle	Mylan Laboratories Ltd	Waluj, Aurangabad, Maharashtra, India	3031904	10 2014	9 2016	Kayonza District Pharmacy	Pharmacy, level 2, public / Eastern	Controlled, 26°C	2	2	Not registered (central supply to government centres)	White, round shaped tablets, debossed "M" on one side of the tablet and score line on the other side, with "LZ" debossed to the left and "1" to the right of the score line	✓	✓ 96.8	✓ 101.9	✓ No tablet deviated by >±7.5%	✓ at S1 Ø (n=6): lam: 99.7% zid: 100.6%	✓	✓	✓
RW/ LZT/ 006/ 23.nov.2015	60 tablets in plastic bottle	Mylan Laboratories Ltd	Waluj, Aurangabad, Maharashtra, India	3031904	10 2014	9 2016	Bugesera District Pharmacy	Pharmacy, level 2, public / Eastern	Controlled, 26°C	2	2	Not registered (central supply to government centres)	White, round shaped tablets, debossed "M" on one side of the tablet and score line on the other side, with "LZ" debossed to the left and "1" to the right of the score line	✓	✓ 96.3	✓ 101.6	✓ No tablet deviated by >±7.5%	✓ at S1 Ø (n=6): lam: 98.8% zid: 100.7%	✓	✓	✓
RW/ LZT/ 007/ 23.11.2015	60 tablets in plastic bottle	Cipla Ltd	Verna, Goa, India	X40546	7 2014	6 2016	Nyamata District Hospital	Hospital, level 2, public / Eastern	Controlled, 26°C	2	n/a	Not registered (central supply to government centres)	White to off-white round tablets, debossed "DR" on one side and breakline on the other	✓	✓ 96.8	✓ 100.2	✓ No tablet deviated by >±7.5%	✓ at S1 Ø (n=6): lam: 97.2% zid: 98.7%	✓	✓	✓

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✓= complies; ✖= does not comply

Country of collection* / sample code	Pack size	Manufacturer	Manufacturing site	Batch number	Manufacture date	Expiry date	Sampling site	Type of sampling site / region	Storage conditions at sampling site	Shelf life claimed (years)	PQ current approved shelf life (years)	Registration status	Appearance	Identity	Assay %		Uniformity of dosage units	Dissolution	Disintegration	Fineness of dispersion	Conclusion
															Lamivudine	Zidovudine					
RW/ LZT/004/20.11.2015	60 tablets in plastic bottle	Cipla Ltd	Verna, Goa, India	X40546	7 2014	6 2016	Muhima District Hospital, Kigali	Hospital, level 2, public / Kigali	Controlled, 26°C	2	n/a	Not registered (central supply to government centres)	White to off-white round tablets, debossed "DR" on one side and breakline on the other	✓	✓ 96.1	✓ 99.6	✓ No tablet deviated by >±7.5%	✓ at S1 Ø (n=6): lam: 99.5% zid: 100.8%	✓	✓	✓
ZM/ LZT/023/061115	60 tablets in plastic bottle	Cipla Ltd	Verna, Goa, India	GG50124	1 2015	12 2016	University Teaching Hospital, Lusaka	Hospital, level 1, public / Lusaka	Controlled, 21.5°C, 32% RH	2	n/a	Registered	White to off-white round tablets, debossed "DR" on one side and breakline on the other	✓	✓ 96.0	✓ 99.5	✓ No tablet deviated by >±7.5%	✓ at S1 Ø (n=6): lam: 98.6% zid: 99.4%	✓	✓	✓
ZM/ LZT/024/061115	60 tablets in plastic bottle	Cipla Ltd	Verna, Goa, India	GG50124	1 2015	12 2016	Churches Health Association of Zambia, Lusaka	Importer, level 1, NGO / Lusaka	Controlled, 24°C, 32% RH	2	n/a	Registered	White to off-white round tablets, debossed "DR" on one side and breakline on the other	✓	✓ 96.4	✓ 100.0	✓ No tablet deviated by >±7.5%	✓ at S1 Ø (n=6): lam: 98.7% zid: 99.5%	✓	✓	✓
ZM/ LZT/025/051115	60 tablets in plastic bottle	Cipla Ltd	Verna, Goa, India	GG50124	1 2015	12 2016	Isoka District Health Office	Treatment centre, level 2, public / Muchinga	Controlled, 18°C, 34% RH	2	n/a	Registered	White to off-white round tablets, debossed "DR" on one side and breakline on the other	✓	✓ 95.9	✓ 99.3	✓ No tablet deviated by >±7.5%	✓ at S1 Ø (n=6): lam: 98.7% zid: 99.5%	✓	✓	✓

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✓= complies; ✖= does not comply

Lamivudine/zidovudine 30/60 mg tablets

Country of collection */ sample code	Pack size	Manu-facturer	Manu-facturing site	Batch number	Manu-facture date	Expiry date	Sampling site	Type of sampling site / region	Storage conditions at sampling site	Shelf life claimed (years)	PQ current approved shelf life (years)	Registration status	Appearance	Identity	Assay %		Uniformity of dosage units	Dissolution	Conclusion
															Lamivudine	Zidovudine			
BF/ LZT/ 17/ 09112015	60 tablets in plastic bottle	Mylan Laboratories Ltd	Sinnar, Nashik, Maharashtra, India	3031643	10 2014	9 2018	Centrale d'Achat des Médicaments Essentiels Génériques et des Consommables médicaux (CAMEG), ZAD Ouagadougou	Importer, level 1, public / Centre	Controlled, 31.1°C, 33.3% RH	4	5	Not registered (donation)	White, film-coated, round shaped tablets, debossed "M29" on one side and breakline on the other	✓	✓ 95.9	✓ 104.3	✓ No tablet deviated by >±7.5%	✓ at S1 Ø (n=6): lam: 99.2% zid: 102.1%	✓
NG/ LZT/ 05/ 030915	60 tablets in plastic bottle	Mylan Laboratories Ltd	Sinnar, Nashik, Maharashtra, India	3028430	7 2014	6 2018	General Hospital, Rigasa, Kaduna State	Hospital, level 2, public / Kaduna	Controlled, 21°C, 52% RH	4	5	Registered	White, film-coated, round shaped tablets, debossed "M29" on one side and breakline on the other	✓	✓ 95.6	✓ 102.5	✓ No tablet deviated by >±7.5%	✓ at S1 Ø (n=6): lam: 95.2% zid: 103.6%	✓
NG/ LZT/ 11/ 030915	60 tablets in plastic bottle	Mylan Laboratories Ltd	Sinnar, Nashik, Maharashtra, India	3028432	7 2014	6 2018	General Hospital, Ikara, Kaduna State	Hospital, level 2, public / Kaduna	Controlled, 20°C, 51% RH	4	5	Registered	White, film-coated, round shaped tablets, debossed "M29" on one side and breakline on the other	✓	✓ 99.0	✓ 103.6	✓ No tablet deviated by >±7.5%	✓ at S1 Ø (n=6): lam: 96.3% zid: 100.5%	✓
NG/ LZT/ 14/ 090915	60 tablets in plastic bottle	Mylan Laboratories Ltd	Sinnar, Nashik, Maharashtra, India	3031818	10 2014	9 2018	Federal Medical Stores, Oshodi, Lagos State (Govt)	Medical store, level 1, public / Lagos	Controlled, 21°C, 51% RH	4	5	Registered	White, film-coated, round shaped tablets, debossed "M29" on one side and breakline on the other	✓	✓ 97.6	✓ 102.6	✓ No tablet deviated by >±7.5%	✓ at S1 Ø (n=6): lam: 96.8% zid: 102.7%	✓
NG/ LZT/ 15/ 090915	60 tablets in plastic bottle	Mylan Laboratories Ltd	Sinnar, Nashik, Maharashtra, India	3031819	10 2014	9 2018	Federal Medical Stores, Oshodi, Lagos State (Govt)	Medical store, level 1, public / Lagos	Controlled, 21°C, 52% RH	4	5	Registered	White, film-coated, round shaped tablets, debossed "M29" on one side and breakline on the other	✓	97.1%	✓ 100.5	✓ No tablet deviated by >±7.5%	✓ at S1 Ø (n=6): lam: 99.8% zid: 101.4%	✓
NG/ LZT/ 18/ 100915	60 tablets in plastic bottle	Mylan Laboratories Ltd	Sinnar, Nashik, Maharashtra, India	3031819	10 2014	9 2018	Lagoon Hospital, Ikeja, Lagos State	Hospital, level 2, private / Lagos	Controlled, 20°C, 51% RH	4	5	Registered	White, film-coated, round shaped tablets, debossed "M29" on one side and breakline on the other	✓	✓ 97.0	✓ 101.7	✓ No tablet deviated by >±7.5%	✓ at S1 Ø (n=6): lam: 100.1% zid: 101.5%	✓

**zid.=zidovudine; nev.=nevirapine, lam.=lamivudine; imp.=impurity

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✓= complies; ✖= does not comply

Lamivudine/zidovudine 150/300 mg tablets

Country of collection */ sample code	Pack size	Manu-facturer	Manu-facturing site	Batch number	Manu-facture date	Expiry date	Sampling site	Type of sampling site / region	Storage conditions at sampling site	Shelf life claimed (years)	PQ current approved shelf life (years)	Registration status	Appearance	Identity	Assay %		Uniformity of dosage units	Dissolution	Conclusion
															Lamivudine	Zidovudine			
BF/ LZT/ 21/ 13112015	60 tablets in plastic bottle	Cipla Ltd	Verna, Goa, India	X30522	6 2013	5 2016	Association des Femmes africaines face au SIDA (AFAFSI), Ouagadougou	Treatment centre, level 2, private / Centre	Not controlled, 32°C	3	3	Not registered (supplied on special permission)	White to off white film-coated, oblong shaped tablets, debossed "DVR" on one side and plain on the other	✓	✓ 99.8	✓ 103.3	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): lam: 98.1% zid: 97.7%	✓
BF/ LZT/ 22/ 10112015	60 tablets in plastic bottle	Macleods Pharmaceuticals Ltd	Baddi, Village Theda, Lodhimajra, Solan, Himachal Pradesh, India	BLE5401-A	12 2014	11 2017	Centrale d'Achat des Médicaments Essentiels Génériques et des Consommables médicaux (CAMEG), ZAD Ouagadougou	Importer, level 1, public / Centre	Controlled, 31.1°C, 33.3% RH	3	3	Registered	White film-coated tablets, oblong shaped, debossed "ML 6" on one side and score line on the other	✓	✓ 96.2	✓ 98.4	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): lam: 99.1% zid: 99.9%	✓
BF/ LZT/ 23/ 16112015	60 tablets in plastic bottle	Hetero Labs Ltd	Jeedimetla, Hyderabad, Andhra Pradesh, India	E141484	8 2014	7 2017	Regional Hôpital de jour (HDJ), Dédougou	Hospital, level 2, public / Boucle de Mouhoun	Not controlled	3	3	Not registered (donation)	White film-coated, oblong shaped tablets, debossed "H" and score line on one side and debossed "2" on the other	✓	✓ 99.5	✓ 103.1	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): lam: 98.6% zid: 99.0%	✓
BF/ LZT/ 24/ 10112015	60 tablets in plastic bottle	Strides Arcolab Ltd	Suraga-jakkanahalli, Indlawadi Cross, Anekal Taluk, Bangalore, Karnataka, India	7222483	9 2014	8 2017	Centrale d'Achat des Médicaments Essentiels Génériques et des Consommables médicaux (CAMEG), ZAD Ouagadougou	Importer, level 1, public / Centre	Controlled, 17°C	3	3	Registered	White film tablets, oval shaped, debossed "LZ" on one side and breakline on the other	✓	✓ 98.4	✓ 102.7	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): lam: 100.0% zid: 100.1%	✓

**zid.=zidovudine; nev.=nevirapine, lam.=lamivudine; imp.=impurity

* BF = Burkina Faso, DRC = Democratic Republic of the Congo, NG = Nigeria, RW = Rwanda, ZM = Zambia

✓= complies; ✖= does not comply

Country of collection */ sample code	Pack size	Manu-facturer	Manu-facturing site	Batch number	Manu-facture date	Expiry date	Sampling site	Type of sampling site / region	Storage conditions at sampling site	Shelf life claimed (years)	PQ current approved shelf life (years)	Registration status	Appearance	Identity	Assay %		Uniformity of dosage units	Dissolution	Conclusion
															Lamivudine	Zidovudine			
BF/ LZT/ 25/ 10112015	60 tablets in plastic bottle	Mylan Laboratories Ltd	Waluj, Aurangabad, Maharashtra, India	3030104	8 2014	7 2019	Centrale d'Achat des Médicaments Essentiels Génériques et des Consommables médicaux (CAMEG), ZAD Ouagadougou	Importer, level 1, public / Centre	Controlled, 31.1°C, 33.3% RH	5	5	Registered	White film-coated, oblong shaped tablets, debossed "M103" on one side and plain on the other	✓	✓ 100.4	✓ 102.9	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): lam: 99.8% zid: 101.0%	✓
DRC/ LZT/ 27/ 10-11-15	60 tablets in plastic bottle	Ranbaxy Laboratories Ltd (Sun Pharmaceutical Industries Ltd)	Paonta Sahib, Sirmaur, Himachal Pradesh, India	2656754	11 2014	10 2016	Centrale d'Achat des Médicaments Essentiels de Kisangani (CAMEKIS), Kisangani	Medical store, level 2, NGO / Tshopo	Controlled, 25.3°C, 53% RH	2	3	Not registered (supplied on special permission)	White film-coated tablets, oblong shaped, debossed "RX923" on one side and plain on the other	✓	✓ 99.5	✓ 103.1	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): lam: 101.0% zid: 102.0%	✓
DRC/ LZT/ 04/ 27-10-15	60 tablets in plastic bottle	Mylan Laboratories Ltd	Waluj, Aurangabad, Maharashtra, India	3017661	9 2013	8 2018	Bolloré Transport & Logistics, Bobozo, Kinshasa	Medical store, level 1, private / Kinshasa	Controlled, 21°C, 56% RH	5	5	Not registered (supplied on special permission)	White film-coated, oblong shaped tablets, debossed "M103" on one side and plain on the other	✓	✓ 95.8	✓ 97.7	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): lam: 98.8% zid: 100.5%	✓
DRC/ LZT/ 07/ 27-10-15	60 tablets in plastic bottle	Hetero Labs Ltd	Jeedimetla, Hyderabad, Andhra Pradesh, India	E140861	5 2014	4 2017	Centrale d'Achat des Médicaments Essentiels de Kinshasa (CAMESKIN), Kinshasa	Medical store, level 1, NGO / Kinshasa	Controlled, 29.5°C, 51% RH	3	3	Not registered (supplied on special permission)	White film-coated, oblong shaped tablets, debossed "H" and score line on one side and debossed "2" on the other	✓	✓ 96.2	✓ 100.5	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): lam: 101.3% zid: 101.1%	✓
DRC/ LZT/ 14/ 10-11-15	60 tablets in plastic bottle	Hetero Labs Ltd	Jeedimetla, Hyderabad, Andhra Pradesh, India	E142173	12 2014	11 2017	Centrale d'Achat des Médicaments Essentiels de Lubumbashi (CAMELU), Katanga	Medical store, level 1, NGO / Haut-Katanga	Controlled, 24°C, 52% RH	3	3	Not registered (supplied on special permission)	White film-coated, oblong shaped tablets, debossed "H" and score line on one side and debossed "2" on the other	✓	✓ 97.1	✓ 102.7	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): lam: 101.4% zid: 101.5%	✓

**zid.=zidovudine; nev.=nevirapine, lam.=lamivudine; imp.=impurity
* BF = Burkina Faso, DRC = Democratic Republic of the Congo, NG = Nigeria, RW = Rwanda, ZM = Zambia

✓= complies; ✖= does not comply

Country of collection */ sample code	Pack size	Manu-facturer	Manu-facturing site	Batch number	Manu-facture date	Expiry date	Sampling site	Type of sampling site / region	Storage conditions at sampling site	Shelf life claimed (years)	PQ current approved shelf life (years)	Registration status	Appearance	Identity	Assay %		Uniformity of dosage units	Dissolution	Conclusion
															Lamivudine	Zidovudine			
DRC/ LZT/ 22/ 06-11-15	60 tablets in plastic bottle	Strides Arcolab Ltd	Suraga-jakkanahalli, Indlawadi Cross, Anekal Taluk, Bangalore, Karnataka, India	7224514	6 2015	5 2018	Bureau Diocésain des Oeuvres Médicales (BDOM), Bukavu	Medical store, level 2, NGO / South Kivu	Controlled, 22°C, 60% RH	3	3	Not registered (supplied on special permission)	White film tablets, oval shaped, debossed "LZ" on one side and breakline on the other	✓	✓ 97.0	✓ 102.1	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): lam: 99.7% zid: 100.3%	✓
NG/ LZT/ 04/ 030915	60 tablets in plastic bottle	Hetero Labs Ltd	Jeedimetla, Hyderabad, Andhra Pradesh, India	E140821	5 2014	4 2017	General Hospital, Rigasa, Kaduna State	Hospital, level 2, public / Kaduna	Controlled, 21°C, 53% RH	3	3	Registered	White film-coated, oblong shaped tablets, debossed "H" and score line on one side and debossed "2" on the other	✓	✓ 99.1	✓ 102.0	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): lam: 98.3% zid: 98.0%	✓
NG/ LZT/ 06/ 090915	60 tablets in plastic bottle	Hetero Labs Ltd	Jeedimetla, Hyderabad, Andhra Pradesh, India	E140860	5 2014	4 2017	Federal Medical Stores, Oshodi, Lagos State (Govt)	Medical store, level 1, public / Lagos	Controlled, 21°C, 52.5% RH	3	3	Registered	White film-coated, oblong shaped tablets, debossed "H" and score line on one side and debossed "2" on the other	✓	✓ 98.1	✓ 102.0	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): lam: 100.7% zid: 100.7%	✓
NG/ LZT/ 08/ 090915	60 tablets in plastic bottle	Aurobindo Pharma Ltd	Bachupally Village, Ranga Reddy, Telangana, India	IZ1515003-A	2 2015	1 2018	Federal Medical Stores, Oshodi, Lagos State (Govt)	Medical store, level 1, public / Lagos	Controlled, 21°C, 51.2% RH	3	n/a	Registered	Off white film-coated, oblong shaped tablet, debossed "C 60" on one side and plain on the other	✓	✓ 95.5	✓ 100.0	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): lam: 99.4% zid: 100.1%	✓
NG/ LZT/ 13/ 020915	60 tablets in plastic bottle	Hetero Labs Ltd	Jeedimetla, Hyderabad, Andhra Pradesh, India	E141951	10 2014	9 2017	Rural Health Hospital, Zonkwa, Kaduna State	Hospital, level 2, public / Kaduna	Controlled, 23°C, 52% RH	3	3	Registered	White film-coated, oblong shaped tablets, debossed "H" and score line on one side and debossed "2" on the other	✓	✓ 98.4	✓ 102.7	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): lam: 97.4% zid: 98.2%	✓

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✓= complies; ✖= does not comply

Country of collection */ sample code	Pack size	Manu-facturer	Manu-facturing site	Batch number	Manu-facture date	Expiry date	Sampling site	Type of sampling site / region	Storage conditions at sampling site	Shelf life claimed (years)	PQ current approved shelf life (years)	Registration status	Appearance	Identity	Assay %		Uniformity of dosage units	Dissolution	Conclusion
															Lamivudine	Zidovudine			
NG/ LZT/ 16/ 100915	60 tablets in plastic bottle	Mylan Laboratories Ltd	Sinnar, Nashik, Maharashtra, India	3021562	10 2013	11 2016	Lagoon Hospital, Ikeja, Lagos State	Hospital, level 2, private / Lagos	Controlled, 21°C, 53% RH	3	5	Registered	White film-coated, oblong shaped tablets, debossed "M103" on one side and plain on the other	✓	✓ 99.3	✓ 100.8	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): lam: 99.2% zid: 100.8%	✓
RW/ LZT/ 003/ 20.nov.2015	60 tablets in plastic bottle	Hetero Labs Ltd	Jeedimetla, Hyderabad, Andhra Pradesh, India	E142173	12 2014	11 2017	Medical Procurement and Production Division (MPPD), Kigali	Medical store, level 1, public / Kigali	Controlled, 25°C	3	3	Not registered (central supply to government centres)	White film-coated, oblong shaped tablets, debossed "H" and score line on one side and debossed "2" on the other	✓	✓ 96.7	✓ 100.5	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): lam: 99.3% zid: 100.6%	✓
RW/ LZT/ 001/ 18.nov.2015	60 tablets in plastic bottle	Ranbaxy Laboratories Ltd (Sun Pharmaceutical Industries Ltd)	Paonta Sahib, Sirmaur, Himachal Pradesh, India	2623748	7 2014	6 2016	Kayonza District Pharmacy	Pharmacy, level 2, public / Eastern	Controlled, 26°C	2	3	Not registered (central supply to government centres)	White film-coated, oblong shaped tablets, debossed "RX 923" on one side and plain on the other	✓	✓ 96.4	✓ 101.7	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): lam: 98.7% zid: 101.2%	✓
RW/ LZT/ 006/ 23.nov.2015	60 tablets in plastic bottle	Ranbaxy Laboratories Ltd (Sun Pharmaceutical Industries Ltd)	Paonta Sahib, Sirmaur, Himachal Pradesh, India	2623754	7 2014	6 2016	Bugesera District Pharmacy	Pharmacy, level 2, public / Eastern	Controlled, 26°C	2	3	Not registered (central supply to government centres)	White film-coated, oblong shaped tablets, debossed "RX 923" on one side and plain on the other	✓	✓ 97.5	✓ 102.1	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): lam: 100.3% zid: 100.3%	✓
RW/ LZT/ 005/ 20.11.2015	60 tablets in plastic bottle	Ranbaxy Laboratories Ltd (Sun Pharmaceutical Industries Ltd)	Paonta Sahib, Sirmaur, Himachal Pradesh, India	2618821	6 2014	5 2016	Kinyinya Health Facility	Treatment centre, level 2, public / Kigali	Controlled, 24°C	2	3	Not registered (central supply to government centres)	White film-coated, oblong shaped tablets, debossed "RX 923" on one side and plain on the other	✓	✓ 98.6	✓ 102.1	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): lam: 100.2% zid: 101.4%	✓

**zid.=zidovudine; nev.=nevirapine, lam.=lamivudine; imp.=impurity

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✓= complies; ✖= does not comply

Country of collection */ sample code	Pack size	Manu-facturer	Manu-facturing site	Batch number	Manu-facture date	Expiry date	Sampling site	Type of sampling site / region	Storage conditions at sampling site	Shelf life claimed (years)	PQ current approved shelf life (years)	Registration status	Appearance	Identity	Assay %		Uniformity of dosage units	Dissolution	Conclusion
															Lamivudine	Zidovudine			
RW/ LZT/ 004/ 20.11.2015	60 tablets in plastic bottle	Ranbaxy Laboratories Ltd (Sun Pharmaceutical Industries Ltd)	Paonta Sahib, Sirmaur, Himachal Pradesh, India	2623752	7 2014	6 2016	Muhima District Hospital, Kigali	Hospital, level 2, public / Kigali	Controlled, 26°C	2	3	Not registered (central supply to government centres)	White film-coated, oblong shaped tablets, debossed "RX 923" on one side and plain on the other	✓	✓ 97.9	✓ 101.2	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): lam: 99.1% zid: 101.0%	✓
ZM/ LZT/ 002/ 021115	60 tablets in plastic bottle	Aurobindo Pharma Ltd	Bachupally Village, Ranga Reddy, Telangana, India	LZ1514 034-B	6 2014	5 2017	Ndola Central Hospital	Hospital, level 2, public / Copperbelt	Controlled, 27.9°C, 42% RH	3	n/a	Registered	Off white film-coated, oblong shaped tablet, debossed "C 60" on one side and plain on the other	✓	✓ 99.2	✓ 102.9	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): lam: 98.7% zid: 102.9%	✓
ZM/ LZT/ 026/ 061115	60 tablets in plastic bottle	Hetero Labs Ltd	Polepally Village, Mahaboob Nagar, Andhra Pradesh, India	LAZ114 013	9 2014	8 2017	University Teaching Hospital, Lusaka	Hospital, level 1, public / Lusaka	Controlled, 21.5°C, 32% RH	3	3	Registered	White film-coated, oblong shaped tablets, debossed "H" and score line on one side and debossed "2" on the other	✓	✓ 95.4	✓ 101.3	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): lam: 93.7% zid: 94.7%	✓
ZM/ LZT/ 027/ 061115	60 tablets in plastic bottle	Cipla Ltd	Verna, Goa, India	GG4529 2	12 2014	11 2017	Prime Pharmaceuticals Ltd, Lusaka	Importer, level 1, private / Lusaka	Controlled, 22°C, 32% RH	3	3	Registered	White to off white film-coated, oblong shaped tablets, debossed "DVR" on one side and plain on the other	✓	✓ 96.0	✓ 98.7	✓ No tablet deviated by >±5%	Complies at S1 Ø (n=6): lam: 99.4% zid: 99.8%	✓
ZM/ LZT/ 028/ 031115	60 tablets in plastic bottle	Strides Arcolab Ltd	Suraga-jakkanahalli, Indlawadi Cross, Anekal Taluk, Bangalore, Karnataka, India	7220553	12 2013	11 2016	Chikankata Mission Hospital	Hospital, level 2, NGO / Southern	Controlled, 25°C, 34% RH	3	3	Registered	White film tablets, oval shaped, debossed "LZ" on one side and breakline on the other	✓	✓ 97.6	✓ 100.7	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): lam: 100.6% zid: 99.3%	✓

**zid.=zidovudine; nev.=nevirapine, lam.=lamivudine; imp.=impurity

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Country of collection */ sample code	Pack size	Manu-facturer	Manu-facturing site	Batch number	Manu-facture date	Expiry date	Sampling site	Type of sampling site / region	Storage conditions at sampling site	Shelf life claimed (years)	PQ current approved shelf life (years)	Registration status	Appearance	Identity	Assay %		Uniformity of dosage units	Dissolution	Conclusion
															Lamivudine	Zidovudine			
ZM/ LZT/ 029/ 021115	60 tablets in plastic bottle	Hetero Labs Ltd	Polepally Village, Mahaboob Nagar, Andhra Pradesh, India	LAZ114013	9 2014	8 2017	Siavonga District Hospital	Hospital, level 2, public / Southern	Controlled, 25°C, 45% RH	3	3	Registered	White film-coated, oblong shaped tablets, debossed "H" and score line on one side and debossed "2" on the other	✓	✓ 97.2	✓ 101.5	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): lam: 89.2% zid: 88.3%	✓
ZM/ LZT/ 030/ 031115	60 tablets in plastic bottle	Hetero Labs Ltd	Polepally Village, Mahaboob Nagar, Andhra Pradesh, India	LAZ114026	10 2014	9 2017	Mpongwe District Health Office, Ndola Rural	Treatment centre, level 2, public / Copperbelt	Controlled, 24°C, 40% RH	3	3	Registered	White film-coated, oblong shaped tablets, debossed "H" and score line on one side and debossed "2" on the other	✓	✓ 100.7	✓ 104.9	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): lam: 96.0% zid: 95.3%	✓
ZM/ LZT/ 031/ 061115	60 tablets in plastic bottle	Hetero Labs Ltd	Jeedimetla, Hyderabad, Andhra Pradesh, India	E150142	1 2015	12 2017	Medical Stores Ltd, Lusaka	Medical store, level 1, public / Lusaka	Controlled, 24°C, 31% RH	3	3	Registered	White film-coated, oblong shaped tablets, debossed "H" and score line on one side and debossed "2" on the other	✓	✓ 99.1	✓ 102.1	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): lam: 101.4% zid: 101.1%	✓
ZM/ LZT/ 032/ 061115	60 tablets in plastic bottle	Strides Arcolab Ltd	Suraga-jakkanahalli, Indlawadi Cross, Anekal Taluk, Bangalore, Karnataka, India	7220553	12 2013	11 2016	Churches Health Association of Zambia, Lusaka	Importer, level 1, NGO / Lusaka	Controlled, 24°C, 32% RH	3	3	Registered	White film tablets, oval shaped, debossed "LZ" on one side and breakline on the other	✓	✓ 97.9	✓ 101.0	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): lam: 100.6% zid: 99.3%	✓
ZM/ LZT/ 033/ 061115	60 tablets in plastic bottle	Mylan Laborato-ries Ltd	Sinnar, Nashik, Maharashtra, India	3029578	8 2014	7 2017	Gwembe District Hospital	Hospital, level 2, public / Southern	Controlled, 18°C, 38% RH	3	5	Registered	White film-coated, oblong shaped tablets, debossed "M103" on one side and plain on the other	✓	✓ 98.1	✓ 103.5	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): lam: 101.0% zid: 102.7%	✓

**zid.=zidovudine; nev.=nevirapine, lam.=lamivudine; imp.=impurity

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Country of collection */ sample code	**Pack size**	**Manu-facturer**	**Manu-facturing site**	**Batch number**	**Manu-facture date**	**Expiry date**	Sampling site	Type of sampling site / region	Storage conditions at sampling site	Shelf life claimed (years)	PQ current approved shelf life (years)	Registration status	**Appearance**	**Identity**	**Assay %**		**Uniformity of dosage units**	**Dissolution**	**Conclusion**
															Lamivudine	**Zidovudine**			
ZM/ LZT/ 034/ 041115	60 tablets in plastic bottle	Hetero Labs Ltd	Polepally Village, Mahaboob Nagar, Andhra Pradesh, India	LAZ114027	11 2014	10 2017	Kasama General Hospital	Hospital, level 2, public / Northern	Controlled, 29°C, 32% RH	3	3	Registered	White film-coated, oblong shaped tablets, debossed "H" and score line on one side and debossed "2" on the other	✓	✓ 99.1	✓ 103.4	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): lam: 95.3% zid: 94.9%	✓
ZM/ LZT/ 035/ 031115	60 tablets in plastic bottle	Aurobindo Pharma Ltd	Bachupally Village, Ranga Reddy, Telangana, India	LZ1514037-A	6 2014	5 2017	Livingstone General Hospital	Hospital, level 2, public / Southern	Controlled, 28°C, 36% RH	3	n/a	Registered	Off white film-coated, oblong shaped tablet, debossed "C 60" on one side and plain on the other	✓	✓ 96.0	✓ 100.0	✓ No tablet deviated by >±5%	✓ at S1 Ø (n=6): lam: 98.0% zid: 98.7%	✓

**zid.=zidovudine; nev.=nevirapine, lam.=lamivudine; imp.=impurity

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Appendix 8 Nevirapine 50 mg dispersible tablets – test results

Specifications:

Assay: 90.0-110.0%
Uniformity of dosage units: according to USP ⟨905⟩ - Weight variation
Dissolution: NLT 75%(Q) in 60 minutes

Country of collection*/ sample code	Pack size	Manu-facturer	Manu-facturing site	Batch number	Manu-facture date	Expiry date	Sampling site	Type of sampling site / region	Storage conditions at sampling site	Shelf life claimed (years)	PQ current approved shelf life (years)	Registration status	Appearance	Identity	Assay	Uniformity of dosage units	Dissolution	Disintegration	Fineness of dispersion	Conclusion
DRC/ NEV/ 01/ 27-10-15	30 tablets in plastic bottle	Aurobindo Pharma Ltd	Bachupally Village, Ranga Reddy, Telangana, India	NB501 4010-A	11 2014	10 2016	Bolloré Transport & Logistics, Bobozo, Kinshasa	Medical store, level 1, private / Kinshasa	Controlled, 21°C, 56% RH	2	n/a	Not registered (supplied on special permission)	Round, white tablets, debossed "I" on one side, on the other side a breakline with "4" debossed on one side and "7" on the other	✓	✓ 96.1	✓ AV (n=10): 4.6	✓ at S1 Ø (n=6): 101.8%	✓	✓	✓
DRC/ NEV/ 19/ 05-11-15	30 tablets in plastic bottle	Aurobindo Pharma Ltd	Bachupally Village, Ranga Reddy, Telangana, India	NB501 4009-A	11 2014	10 2016	Association Régionale d'Approvisionnement en Médicaments Essentiels (ASRAMES), Goma	Medical store, level 1, NGO / North Kivu	Controlled, 23.4°C, 59% RH	2	n/a	Not registered (supplied on special permission)	Round, white tablets, debossed "I" on one side, on the other side a breakline with "4" debossed on one side and "7" on the other	✓	✓ 96.6	✓ AV (n=10): 4.7	✓ at S1 Ø (n=6): 101.7%	✓	✓	✓
DRC/ NEV/ 24/ 06-11-15	30 tablets in plastic bottle	Aurobindo Pharma Ltd	Bachupally Village, Ranga Reddy, Telangana, India	NB501 4009-A	11 2014	10 2016	Bureau Diocésain des Oeuvres Médicales (BDOM), Bukavu	Medical store, level 2, NGO / South Kivu	Controlled, 22°C, 60% RH	2	n/a	Not registered (supplied on special permission)	Round, white tablets, debossed "I" on one side, on the other side a breakline with "4" debossed on one side and "7" on the other	✓	✓ 100.0	✓ AV (n=10): 3.9	✓ at S1 Ø (n=6): 101.5%	✓	✓	✓

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This quality survey was organized during 2015 and 2016 by the WHO Prequalification Team in cooperation with the National Medicines Regulatory Authorities/Ministries of Health in five countries in Sub-Saharan Africa: Burkina Faso, Democratic Republic of the Congo, Nigeria, Rwanda, Nigeria and Zambia. The objective of the survey was to assess the quality of selected antiretroviral medicines (ARVs) obtained at approved (authorized or accredited) public and private sector procurement and treatment sites.

Medicines samples were collected at official public and private procurement and treatment centres. The survey targeted selected ARVs used in large volumes, those products with the highest probability of quality problems, paediatric formulations for which there had been a steady increase in prequalification in the previous five years; and products of which substandard or falsified versions had been reported to the WHO Global Surveillance System.

Of the 126 samples tested, 125 complied with the specifications set for the survey. A failure rate of 0.8%.

The survey provided a snapshot of the quality of the sampled products and generated information about the availability of the target medicines in selected countries, their prequalification and registration status, and the storage conditions in procurement and treatment centres in participating countries. The share of prequalified products among samples increased from 53% to 98% relative to previous surveys. The survey reconfirmed the positive impact of WHO prequalification in making products of consistently good quality available for procurement in countries.

The survey results further indicate that storage conditions in procurement and treatment centres in participating countries were in principle under control and did not have a negative impact on medicines quality.

The method of multistate collaborative sampling and centralized testing with common data analysis has once more proved to be a useful approach in independent quality monitoring of prioritized medicines. The approach was commended by participating countries that also recommended for future surveys to incorporate non-destructive screening during sampling as well as parallel in-country testing of samples in national quality control laboratories.



PREQUALIFICATION TEAM: MEDICINES AND REGULATORY SYSTEMS STRENGTHENING REGULATION OF MEDICINES AND OTHER HEALTH TECHNOLOGIES

DEPARTMENT OF ESSENTIAL MEDICINES AND HEALTH PRODUCTS

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