Quality monitoring

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

This article presents an overview of the findings of a sample testing survey organized by WHO as part of its quality monitoring activities for medicines. The survey confirmed the positive impact of WHO prequalification in assuring the quality of antiretrovirals used in HIV treatment programmes of WHO Member States. A full report of the survey is in preparation.

Introduction
A quality survey was organized in 2015 and 2016 by the WHO Prequalification Team (WHO-PQT) in cooperation with the National Medicines Regulatory Authorities/Ministries of Health in five countries in Sub-Saharan Africa. 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.

This is the fifth survey of this nature organized by WHO-PQT. Reports of previous surveys are available on the WHO website. (1,2,3,4) The survey results are intended to assist the responsible authorities in participating countries to evaluate their markets and propose possible strategies and implementation plans to address any problems identified. In addition, the active engagement of regulatory staff is expected to help build capacity for coordinated post-market quality surveillance in WHO Member States.

Methodology
Medicines samples were collected at official public and private sector procurement and treatment centres in Burkina Faso, Democratic Republic of the Congo (DRC), Nigeria, Rwanda and Zambia. The survey targeted selected ARVs used in large volumes as reported by international procurers. The focus was on those products with the highest probability of quality problems, prioritizing paediatric formulations – for which there has been a steady increase in prequalification in the past five years – and products of which substandard or falsified versions had been reported to the WHO Global Surveillance System. (5) The following ARVs were included in the survey:

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

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- lamivudine/nevirapine/zidovudine 150/200/300mg tablets;
- lamivudine/zidovudine 30/60mg dispersible tablets;
- lamivudine/zidovudine 30/60mg tablets;
- lamivudine/zidovudine 150/300mg tablets; and
- nevirapine 50mg dispersible tablets.

The quality of the samples was verified by testing at four WHO-prequalified laboratories according to the monographs of The International Pharmacopoeia, British Pharmacopoeia and US Pharmacopeia as applicable. Testing according to official pharmacopoeial monographs made it possible to compare products from different manufacturers. However, individual products may be registered in countries or prequalified by WHO with methods and specifications that differ from those set for this survey. The protocol therefore required that if a sample of a prequalified product was found to be out of specification when using the pharmacopoeial method, it was to be re-tested using the manufacturer's validated method accepted by WHO-PQT. The decision on compliance was then based on the result of the method used in the re-testing.

The survey was conducted in good compliance with the pre-established protocol. As in previous surveys organized by WHO-PQT, the outcomes were discussed with representatives of regulatory authorities, who participated in the formulation of recommendations.

Results

Number of samples tested
A total of 126 samples were collected and tested.

Origin of samples
The samples collected represented medicines produced by eight different manufacturers, all of whom were based in India. The authenticity in terms of batch number, manufacturing and expiry dates, and manufacturing site was confirmed for all samples by the relevant manufacturers. Therefore it is highly unlikely that any falsified products were present among the collected samples. The large majority of samples (98%, 123 of 126 samples) were of WHO-prequalified products.

Testing results
Of the 126 samples tested, 125 fully complied with the specifications set for the survey. This included two samples that did not comply with pharmacopoeial specifications during initial testing, but complied when re-tested with approved manufacturer's methods.

There was only one non-compliant finding in the survey: In one of two collected containers of a sample the tablets were stained with drying agent from a burst sachet, causing them to fail the pharmacopoeial requirements for appearance. The stained tablets were excluded from further testing.

Discussion
The survey provided a snapshot picture 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.

Testing at WHO-prequalified laboratories according to the common protocol and specifications can be considered as reliable.
However, when interpreting the outcomes of the survey 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 taken at official procurement and treatment centres.

The survey showed that pharmacopoeial methods are not always applicable for quality control of specific products. Although in the majority of cases they seemed to be sufficient to control products appropriately, there were two cases where – contrary to the approved manufacturers’ methods – they provided marginally failing results.

Compared with the results of the study organized by WHO-PQT in 2007,(1) the failure rate decreased from 1.8% to 0.8%, indicating a marginal improvement of the quality of ARVs found in official distribution and treatment centres. The share of prequalified products among samples increased from 53% to 98%. The survey reconfirmed the positive impact of WHO prequalification in making ARVs of consistently good quality available for procurement in countries.

In the five quality surveys organized to date by WHO-PQT across product categories, 113 of 682 non-prequalified product samples failed to comply with specifications, compared with only seven of 464 WHO-prequalified product samples. For two of the seven it could be shown that the problem was likely caused after manufacture.(2) These results demonstrate that WHO prequalification reliably assures uniform quality standards.

ARVs procured for HIV treatment programmes are mostly donor- or government-funded, and are typically subject to quality policies that require them to be WHO-prequalified or approved for use in a stringent regulatory environment. As can be expected, all the samples collected in the survey were of imported products, none of them represented locally produced medicines.

The complexity of procurement and distribution of ARVs was illustrated by the fact that some manufacturers did not know to which markets their products were supplied in the end, and re-distribution of medicines among countries was frequent. This highlights the importance for regulators to take into account the risks associated with such complex supply channels.

In principle, the selected medicines were available at procurement and treatment centres, although there were differences in the number of generic versions that were available. For certain medicines targeted in the survey the availability was influenced by local therapeutic guidelines and practices.

Rigorous registration policies are applied in some participating countries – notably in Nigeria and Zambia – but other legally acceptable mechanisms that bypass normal registration processes are also used to ensure a continued supply of needed medicines, as was the case in Burkina Faso, DRC and Rwanda. It was not assessed to which extent the responsible national authorities verified whether the ARVs targeted in this survey were in line with the specifications and conditions accepted by WHO-PQT, for example by using the WHO collaborative registration procedure.(6) Four of the five countries included in the survey (Burkina Faso, DRC, Nigeria and Zambia) were participating in the collaborative procedure at the time of the study. However, only two products registered through this pathway were sampled in the survey, namely lamivudine 150mg tablets and lamivudine/zidovudine 150/300mg tablets in Nigeria.

1 A list of collaboratively registered products is available at https://extranet.who.int/prequal/content/collaborative-registration-faster-registration.
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.

**Conclusions and recommendations**

Although antiretrovirals with a higher probability of substandard quality were targeted in this survey, the results indicate that ARVs available at official procurement and treatment sites are of good quality.

The method of multistate collaborative sampling, 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 during the debriefing session.

It was recommended that future surveys should incorporate non-destructive in-country screening before samples are submitted to designated laboratories, and that parallel in-country testing of samples in national quality control laboratories could be conducted as an element of proficiency testing to build capacity and confidence. WHO should also make efforts to develop data-sharing platforms or repositories of testing results for use by Member States.

**References**


