

Removal of Antiretroviral Products from the WHO List of Prequalified Medicines
Information and Guidance for Regulatory Bodies, National AIDS Programmes, Doctors and Patients

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WHO continues to receive many questions on the recent de-listing of five medicines from its list of prequalified products. Given the importance of these medicines for patients and for international efforts to scale up treatment, WHO offers below some clearer explanations for the decision to delist the products concerned, and advice for regulatory bodies, national AIDS programme managers, prescribers and patients on what can be done as a response to this at country level.

WHAT HAS HAPPENED?

In May and July 2004, WHO ran a series of inspections of contract research organizations and/or laboratories (hereafter: CROs) as part of its ongoing monitoring of prequalified medicines. The CROs had been contracted by manufacturers to carry out tests to prove the bioequivalence of medicines submitted for prequalification, in accordance with WHO requirements. Bioequivalence tests are clinical trials conducted in healthy volunteers to find out if the concentration of a generic medicine in the blood of a patient is equivalent to that of the originator product. Originally, the data (results) presented to WHO by the manufacturers did prove bioequivalence.

During the inspections, one CRO was found to be compliant with international guidance on Good Clinical Practice and Good Laboratory Practice in doing these studies. However, two other CROs were not found compliant because of serious discrepancies between the original results compiled by the CROs and the results presented to WHO by the manufacturers.

1. Confirmation of two AIDS medicines' bioequivalence

The CRO which had conducted bioequivalence studies for a triple fixed-dose combination in two different strengths was found compliant. These products (one prequalified in December 2003, the other at the same time as the CRO inspection) are therefore proven to be bioequivalent and can be used as alternatives to two of the recently removed medicines. These are:

- lamivudine 150mg plus stavudine 40 mg and nevirapine 200 mg tablet (Cipla) *already on the list*
- lamivudine 150mg plus stavudine 30 mg and nevirapine 200 mg tablet (Cipla) *recently added*

2. Five HIV/AIDS medicines were removed from the list for lack of proof of bioequivalence

For five medicines, WHO could no longer accept the report on the bioequivalence studies provided by the manufacturers. Since proof of bioequivalence is a condition for prequalification, and in view of the serious nature of the CROs' non-compliance, two of the products concerned were removed from the list on 27 May and three others on 4 August. The five products are:

- Lamivudine 150mg plus stavudine 30mg and nevirapine 200mg tablet (Ranbaxy Laboratories Ltd, Dewas, India, Al strip of 10 or 60 in box)
- Lamivudine 150mg plus stavudine 40mg and nevirapine 200mg tablet (Ranbaxy Laboratories Ltd, Dewas, India, Al strip of 10 or 60 in box)
- Lamivudine 150mg plus zidovudine 300mg tablet (Ranbaxy Laboratories Ltd, Dewas, India, Blister pack of 60 or 100)
- Lamivudine 150mg tablet (Cipla Ltd, Kurkumbh, India, blister pack of 10)
- Lamivudine 150mg plus zidovudine 300mg tablet (Cipla Ltd, Vikhroli, India, blister pack of 10).

WHAT DOES THE REMOVAL OF THE FIVE MEDICINES MEAN?

WHO is not a supranational regulatory authority. The list of WHO prequalified products includes medicines which have been evaluated and approved for procurement by United Nations organizations. That list does not have any legal status at national level. In countries, the full responsibility for authorizing marketing and use of medicinal products in public health programmes rests with the national drug regulatory authority. The standards used by WHO for prequalification are more stringent than those applied by many countries. For example, not all countries legally require *in vivo* bioequivalence studies (small clinical trials conducted in healthy volunteers) for generic drugs; nor do they have stringent requirements for the quality of active pharmaceutical ingredients.

When deciding on the best course of action, national authorities, programmes, prescribers and patients should take the following considerations into account:

- **These products may or may not be bioequivalent;**
- **Interruption of ARV treatment constitutes a serious risk for the individual and may have negative implications from a public health perspective.**

PRACTICAL IMPLICATIONS FOR NATIONAL DRUG REGULATORY AUTHORITIES

Additional explanation

The five products have been removed because proof of bioequivalence is missing as a result of non-compliance with good clinical and laboratory practices. However, they do meet other quality specifications, such as the active pharmaceutical ingredient purity, stability, and manufacture in compliance with Good Manufacturing Practices in a state-of-the-art pharmaceutical plant.

Recommended action

Many national drug regulatory authorities do not require bioequivalence data to admit generic drugs into their markets. In this case there is no legal obligation to withdraw marketing authorization for the five drugs that were removed. In countries where bioequivalence is required, the national drug regulatory authority should consider one or more of the following actions:

- (1) Request a confidential copy of the inspection report(s) from WHO;
- (2) Temporarily waive its requirement of bioequivalence for these products as an emergency measure, requesting that the manufactures submit data on new bioequivalence studies within four months (if these deadlines are not met, consider withdrawing marketing authorization);

- (3) Do not release the products in stock for use until further evidence from new bioequivalence studies becomes available;
- (4) Withdraw marketing authorization for the products;
- (5) Provide detailed information and advice to programme managers, prescribers and patients on the best ways to manage the situation without compromising the goals of treatment programmes.

PRACTICAL IMPLICATIONS FOR PROGRAMME MANAGERS

Additional explanation

In countries where bioequivalence data are not required by the national drug regulatory authority there is no legal need to withdraw the products; and even in countries where these data are required, the authorities may (temporarily) decide not to withdraw them (see above). In all cases, a careful balance must be sought between the risks associated with the lack of proof of bioequivalence in these products and the individual and public health risk of interrupting treatment should no alternative medicines be found.

In general, switching to similar antiretrovirals (ARVs) from alternative, prequalified suppliers would be the most appropriate response, if and when such products are available. (see Annex 1 below) However, switching to non-prequalified ARVs is not advised since not only has their bioequivalence not been confirmed, but, in addition, other quality aspects have not been verified by WHO.

Recommended action

- (1) Consult with the national drug regulatory authority to establish the best course of action.
- (2) Prepare and implement a communication strategy addressed to prescribers and patients.
- (3) Take the necessary measures to switch to alternative prequalified products (listed in Annex 1 below). In this regard, the following actions are recommended in specific situations:
 - (a) **The procurement of de-listed drugs is considered, but they have not yet been ordered.** De-listed products should not be ordered. Instead, other prequalified products should be ordered unless the de-listed medicines are reinstated on WHO's list of prequalified products.
 - (b) **De-listed drugs have been ordered to continue or scale up treatment programmes.** De-listed drugs that have been ordered, but not received, should not be accepted. In this case, alternative prequalified products should be ordered instead. However, if alternative suppliers are not immediately available and the non-acceptance of the ordered products could lead to an inability to continue or to start treating patients, the risk of withholding treatment is higher than that of providing medicines whose bioequivalence is not proven but which have, otherwise, been prequalified. In this case it would be justified to accept and use the de-listed products. For follow-up orders, only prequalified products should be used.

PRACTICAL IMPLICATIONS FOR PRESCRIBERS AND PATIENTS

In principle, patients should discontinue using de-listed medicines and switch to other prequalified products (see Annex 1). However, in many cases it will be difficult to find alternative prequalified products immediately. In this situation it is recommended that patients continue to use de-listed products, as the risk of interrupting treatment is higher

than that of taking medicines whose bioequivalence is not proven but which have otherwise been prequalified. A switch to non-prequalified products is not recommended as their quality has not been documented by WHO.

The patient should be informed that there is no reason to believe continued use of the de-listed products is dangerous, and that suspending the treatment or switching to alternative ARVs whose quality has not been assured is far riskier.

NEXT STEPS

Next steps by the manufacturers

The manufacturers have indicated that they will resubmit the products in question to a different laboratory for new bioequivalence studies. If and when those products and the laboratory meet the specified requirements, WHO will reinstate them in its list of prequalified medicines.

Next steps by WHO

- WHO will make available to national drug regulatory authorities, upon request and under confidential cover, the inspection reports on the de-listed products.
- As soon as new bioequivalence data of the de-listed products have been received WHO will arrange for immediate data assessment and site inspections, to minimize administrative delays in the potential re-listing of the products.
- WHO will send a letter to all manufacturers of prequalified products, asking them to take all necessary measures to ensure that the data submitted to WHO are correct and complete, and to check that CROs have followed the appropriate standards.
- As a matter of urgency, WHO will inspect all other CROs which have conducted bioequivalence studies for prequalified products, starting with priority medicines.
- For new applications, WHO will introduce inspections of CROs and laboratories for compliance with Good Clinical Practice and Good Laboratory Practice as a prerequisite for prequalification.
- WHO will also start a programme of inspections of manufacturers of Active Pharmaceutical Ingredients (raw materials), with an initial focus on antiretrovirals.

FREQUENTLY ASKED QUESTIONS

How is it possible that these de-listed products had been prequalified at all?

Up to now the assessment of bioequivalence data (supplied by the manufacturer) was part of the standard procedure for prequalification; regular on-site inspection of the CROs where the bioequivalence studies were done was not. This reflected common practice in many national Drug Regulatory authorities. On 1 May 2004, European Commission Directive 2001/10/EC came into force, demanding that countries carry out such inspections. Given WHO's commitment to the highest standards, the EC Directive prompted inspections of the CROs carrying out bioequivalence studies (starting with products for priority diseases), which ultimately led to the de-listing of the above five products.

What does it mean for the other products on the list?

All products on the list have been assessed through: evaluation of data in the product dossiers on efficacy, safety, quality and bioequivalence; inspection of manufacturing sites for compliance with good manufacturing practices; and testing of product samples

at independent laboratories for compliance with product specifications. In line with the European Directive of 1 May 2004, good clinical and laboratory practices inspections are now being included in the requirements. For example, a recent inspection at the CRO which did the bioequivalence studies for two different strengths of Cipla's triple combination revealed that good clinical and laboratory practices had been followed and that these products (one prequalified in December 2003 and the other in August 2004) are therefore bioequivalent with the originator medicines.

Many national Drug Regulatory authorities do, from time to time, withdraw a registered product. This does not mean that the original registration was unjustified, but that the verification system is rigorous and that the efficacy, safety and quality of registered products continue to be checked after initial registration.

Further Information

Statements on the removal of products can be found at:

<http://www.who.int/mediacentre/news/releases/2004/pr53/en/>

<http://www.who.int/mediacentre/news/releases/2004/pr53/en/>

http://www.who.int/mediacentre/news/statements/2004/statement_aidsprequal/en/

http://www.who.int/mediacentre/news/statements/2004/statement_aidsprequal/en/

More information on the prequalification project, including a full list of WHO prequalified products, is available at <http://mednet3.who.int/prequal/>

Price information is available from WHO at

<http://www.who.int/medicines/organization/par/ipc/s&pScreen/S&Pscreen.pdf>

from MSF at <http://www.accessmed-msf.org/documents/untanglingtheweb6.pdf>

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ANNEX 1:

ALTERNATIVE PREQUALIFIED MEDICINES AND SUPPLIERS

- Lamivudine 150 mg plus zidovudine 300 mg tablet (GSK), blister (60), bottle (60)
- Lamivudine 150 mg plus zidovudine 300 mg tablet (Hetero), blister (10), bottle (60)
- Lamivudine 150mg plus stavudine 40 mg and nevirapine 200 mg tablet (CIPLA), bottle (60)
- Lamivudine 150mg plus stavudine 30 mg and nevirapine 200 mg tablet (CIPLA), bottle (60)
- Lamivudine 150 mg tablet (GSK), 10 mg/ml oral solution (GSK), bottle (60) and bottle (240 ml), respectively
- Lamivudine 150 mg tablet (Hetero), blister (10), bottle (60)
- Lamivudine 150 mg tablet (Strides), blister (10), bottle (60)