Quality assurance of single and limited source pharmaceuticals:

*Implications of current Global Fund policy*

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A Introduction

1. Under Global Fund policy, starting 1 January 2005, recipients may exclusively procure single and limited source pharmaceuticals, that a) have been found to be acceptable by the WHO Prequalification Project; or b) have been authorized for consumption in their country by a stringent regulatory authority.¹

2. In the Global Fund’s policies, products that are available only from a single supplier, normally the originator company, are referred to as single source products. If in addition to the single supplier there are a limited number of other suppliers, the product is referred to as a limited-source product. Many of the antiretrovirals and antimalarials belong to the latter category.

3. Quality assuring single and limited source products is often more complex than multi-source products. Products in the latter category have a prior history of safe and efficacious use and their product standards are available in the public domain. In contrast with the Global Fund’s policy on single and limited source products, multi-source products therefore only need to comply with the requirements of the National Drug Regulatory Authority (NDRA) in the recipient’s country.²

4. Until the end of this year, acceptance by the recipient country’s NDRA of single and limited source products suffices. Starting January 2005, this is however, as described in section 1 above, no longer possible. This paper analyzes the potential implications of this shift in policy for Global Fund recipients and their ability to access quality single and limited source products at the lowest possible price.

5. The data presented here was collected from the IDA ARV Procurement Services BV (IDA ARV BV), a 100% subsidiary of the International Dispensary Association, the not-for-profit drug procurement service head-quartered in Amsterdam. To date, IDA ARV BV has procured ARVs for numerous Global Fund recipients countries and is, therefore, uniquely positioned to provide key data required to analyze the current policy and its potential implications.

6. IDA ARV BV BV prides itself on its extensive Quality Assurance (QA) and Quality Control (QC) system. Each potential manufacturer must comply with all current GMP
standards, but is also reviewed in terms of sources of raw materials, stability studies, and product specifications. Once product and manufacturer combinations have been approved, detailed specifications - including the source of raw materials - are prepared to ensure that the product will always be manufactured according to the agreed requirements. Extensive monitoring of product quality continues after approval as well. All batches are inspected and assessed on the basis of the manufacturer's Certificate of Analysis and product specifications.

7. The next section briefly reviews the concept of quality assurance as such and describes the context in which the Global Fund policy was developed. Section C analyzes the data collected. Section D draws conclusions in as much as they are relevant for Global Fund recipients and provides suggestions for alternative policy options.

B Global Fund quality assurance policy: history and objectives

8. During its second meeting (held in April 2002), the Board decided that a Procurement Task Force of technical experts be established to provide to the Board recommendations on possible procurement policies. The Task Force subsequently produced a comprehensive report on the basis of which the following policy was adopted by the Board during its Third Meeting:

Provided products are accepted by the NDRA of the recipient's country, any single or limited source product must:

a) Have been found to be acceptable by the UN Procurement Quality and Sourcing Project (also known as the WHO Prequalification Project); or
b) Have been authorized for consumption in their country by a stringent regulatory authority; or

c) Have been authorized by the NDRA in the recipient's country.

Option c) is applicable only until 31 December 2004, after which suppliers must comply with at least one of the two standards set out in a) and b).

9. For a proper intervention, pharmaceutical products must be safe, effective and of suitable quality to ensure predictable therapeutic outcomes. Without consistent drug product quality there is the risk not only for the health of the individual patient but also exacerbating drug resistance and, of course, wasting scarce resources on spurious or sub-standard products. Having in place a quality assurance system spanning from raw materials to patient use helps to assure the desired therapeutic outcomes.

10. The National Drug Regulatory Authority (NDRA) is responsible for the quality of pharmaceuticals on the market in the vast majority of countries. However, "wide differences in the performance of the [...] NRAs of the different countries leads to different outcomes." The Global Fund therefore decided that single and limited source products (unlike multi-source products) must be found "acceptable by the WHO Prequalification Project." In addition, single and limited source pharmaceutical products that are registered for use in their country by a stringent regulatory authority may also be procured.
11. However, due to the fact that the number of sources available under such a policy was rather limited in October 2002 – the UN pre-qualification project had just started and a mere handful products/manufacturers were pre-qualified or registered for use in countries part of ICH/PICs – the Board decided on a “grandfather period”. During this period, which ends at the end of 2004, single and limited source products approved by the local NDRA (e.g., is most cases not a stringent one) would also be an acceptable determinant of quality.\textsuperscript{10} It was hoped and assumed that at the end of this period, sufficient products would be pre-qualified by WHO or registered for use in countries part of ICH/PICs.

12. This “grandfather period” is rapidly coming to an end and the Global Fund should review whether or not the number of single and limited source products available to PRs starting 1 January 2005 is acceptable. If the number is not acceptable, additional decisions by the Board may be needed immediately. The following section attempts to establish whether or not the number is acceptable based on quantitative data.

C Data analysis

13. IDA ARV BV has collected data on a significant number of single and limited source products, all of them ARVs. This data is presented in full in a comprehensive spreadsheet, which is included in annex 1. This section provides explanatory notes relating to Annex 1.

14. When procuring for its clients, the procurement department requests quotations which, among other things, list the following data-points:

   a. Date
   b. Country of destination
   c. Name and technical specifications of the product
   d. Incoterms (2000)
   e. Registered for use in a member country of the PICs or ICH, if applicable
   f. Pre-qualified by WHO, if applicable
   g. Estimated lead-time
   h. Unit price
   i. Quantity
   j. Total price

15. In total, data has been collected on 130 items (consisting of a total of 17 products in 42 different formulations) for Ethiopia, Ghana, Haiti, Honduras, Ivory Coast, Peru and Ukraine. The data is taken from actual quotations as provided by the manufacturer to IDA ARV BV as well as from the MSF document `Untangling the web of price reductions\textsuperscript{11}`.

16. In principle, IDA ARV BV only procures ARVs that are pre-qualified by WHO or registered for use in a PICs or ICH country. However, in the event that no manufacturer is able to meet this criteria, or when one or multiple manufacturers are able to offer a specific product only against unacceptable conditions (including excessive price, unacceptably long lead-time), it would procure from an alternative source. Products of
such an alternative source would, obviously, still need to comply with IDA ARV BVs’ rigorous internal quality assurance requirements.

17. Hence IDA ARV BV is exceptionally well-positioned to provide data to compare products which would fall under the Global Fund’s QA policy which is applicable until the end of this year on the one hand, with products which would fall under the policy applicable starting 1 January 2005 on the other (see section 8 above for details on these policies).

18. Using the data presented in Annex 1, we have recorded the number of available sources, the unit price (US$) and the total price (US$) per formulation, per country. The data is separated into two categories:
   a. Products that complied with the Fund’s QA policy as applicable until 31 December 2004.
   b. Products that complied with the Fund’s QA policy effective from 1 January 2005 and onwards, *had it been effective at the time of procurement.*

19. Before we move on to presenting the conclusions that can be drawn from this analysis, it is important to point at a number of limitations associated with the data:
   a. The data is collected in countries where IDA ARV BV happened to be contracted – a scientific selection procedure has not been applied.
   b. Data is collected on ARVs only. Other single and limited source products such as ACTs have not been included.
   c. The data collected provides only a snap-shot overview of the market for ARVs: It provides details of the products as applied to a *specific country* and on a *specific date* and in accordance with *specific terms and conditions* only. It is, therefore, precarious to extrapolate from these figures.
   d. The patent situation in the countries has *not* been taken into account.
   e. We have referred to the 18th version of list of pre-qualified products, which means that some products listed here as a ‘Other sources’ may have been listed as “WHO pre-qualified product and manufacturer” when the actual quotation was submitted.
   f. In the spreadsheet, three stars (e.g.: ***) are indicated when a product has been pre-qualified by WHO and is registered for use in a PIC/s or ICH country.
   g. The data presented is of a conservative nature. We have always taken the lowest price available for comparisons, even if the products compared do not necessarily meet additional criteria for winning an award. In addition, IDA ARV BV is a highly professional organization that is able to negotiate prices with manufacturers which range among the most competitive available. In other words, when procuring through a less effective system, price-differences are likely to be more significant.
   h. In addition, products listed under the heading ‘Other sources’ in the spreadsheet *do not* include all such sources but are limited to product that have passed successfully, or are about to pass successfully, IDA ARV BVs’ internal quality assurance procedures. Hence the actual number of ‘Other sources’ is larger than listed in Annex 1. The number of available sources is a, therefore, rather conservative number as well.
D Conclusions and recommendations

20. We have analyzed the procurements conducted by IDA ARV BV on behalf of seven Global Fund recipients over the past 12 months by applying the two Global Fund QA policies (before and after 31 December 2004). In doing so, there are two key conclusions that can be drawn regarding availability and price.

21. Firstly, as indicated in table 1 below, had next year’s QA policy applied during the past 12 months, the availability of sources would have been dramatically lower. In fact, 59% of all ARVs procured would have been available from only one source.

22. This has important implications for the procurement and supply management cycle: because of the dependency on few sources, procurement and supply management systems may become much less flexible. In addition, as is pointed out in the next paragraph, this may have a significant impact on prices.

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<tr>
<th>TABLE 1: Availability of ARV formulations during the past 12 months, applying Global Fund policy before and after 31/12/04</th>
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<td>2 sources</td>
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<td>3 or more sources</td>
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23. Secondly, as indicated in table 2 below, the recipients that have contracted IDA ARV BV would have had to pay significantly more for their ARVs had next year’s Global Fund QA policy applied during the past 12 months. In fact, the aggregate procurements of all seven countries would have cost 28%, or US$ 3.840.688,62, more.

<table>
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<th>TABLE 2: Aggregate ARV order size during the past 12 months, applying Global Fund policy before and after 31/12/04</th>
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<td>Total</td>
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24. It should be emphasized that, as indicated in section 18 g & h above, this study is based on conservative data. Had this study been carried out based on data gathered
from less effective procurement organizations, the conclusions would have been more
dramatic.

25. Based on these conclusions, the Board of the Global Fund is strongly recommended to
reconsider its QA policy prior to it becoming effective on 1 January 2005. The decrease
of available sources for single and limited source products is not unlikely to be
substantial, which may result in delayed or even less effective implementation of Global
Fund grants. In addition, the cost of procurements is not unlikely to increase
significantly.

26. If the Board decides to reconsider its policy, it could study the possibility of extending
the grandfather period. However, this may have negative implications on the quality of
products in countries with a weak NDRA. Therefore, in attempt to reduce the risks
associated with poor quality drugs, the Board could consider the following two QA
policy options (separately or combined):

a. In addition to sources registered in PICs/ICH countries or pre-qualified by WHO,
recipients are allowed to procure from manufacturing sites that have been found
GMP-compliant by WHO, meaning they adhere to good manufacturing practices.

b. In addition to sources registered in PICs/ICH countries or pre-qualified by WHO,
recipients are allowed to procure from established (international) procurement
agencies. This would, however, require the Board to agree upon an internationally
accepted definition of the term “established (international) procurement agency”.

G About IDA ARV Procurement Services BV

27. The not-for-profit organization IDA ARV Procurement Services BV (IDA ARV BV) was
established on January 1st 2004 and focuses on facilitating and accelerating access to
quality assured and quality controlled ARVs, HIV tests and diagnostic requirements at
the lowest possible price. Its current clientele primarily consists of Global Fund
recipients, major international NGOs such as Medicines Sans Frontières and World
Bank recipients. IDA ARV BV is a partner of WHO’s AIDS Medicines and Diagnostics
Service, the Clinton HIV/AIDS Initiative, Partners In Health, Management Sciences for
Health, Medicines Sans Frontières and UNDP. For more information, see www.ida-
arv.nl or contact Bianca Kamps at bkamps@ida-arv.nl.

H Annex 1

Sources and prices of ARVs applying Global Fund policy before and after 31-21-04 (in
Excel), Amsterdam, September 24th 2004.
I Endnotes

A

7 The term stringent drug regulatory authority is defined as a regulatory authority in one of the members of the Pharmaceutical Inspection Cooperation Scheme (PIC/S) and/or the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use (Guide to the Global Fund’s Policies on Procurement and Supply Management, The Global Fund: April 2004, p 8)