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Review of product information for selected antiretroviral medicines circulating in five African countries



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Contents

1	Acknowledgements	v
2	Abbreviations	vi
3	Executive summary	vii
4	Introduction	1
5	Rationale for the survey	3
6	Scope of the survey	4
6.1	Objectives of the survey	4
7	Methodology	5
7.1	Main activities	5
7.2	Sample collection	5
7.3	Review of product information	5
7.3.1	Review of product information for the healthcare provider	5
7.3.2	Review of product information for the patient	6
7.4	Evaluation of the format of the product information	6
7.5	Evaluation of the readability, layout and design of patient information leaflets	6
7.5.1	Evaluation tool: EQIP Score	6
7.5.2	Baker Able Leaflet Design (BALD) criteria	7
7.6	Evaluation questionnaire on healthcare providers' awareness, perceptions of quality and use of WHOPARs	7
7.7	Evaluation questionnaire on the acceptance of dispersible tablets for paediatrics	8
8	Results	9
8.1	Overview of the samples collected	9
8.2	Compliance of product information with WHOPAR or Innovator PI	10
8.2.1	Sample eligibility	10
8.2.2	Overall compliance with published WHOPAR information	11
8.2.4	Compliance of medical information in provided SmPCs with WHOPAR SmPCs	13
8.2.5	Collected samples' format compliance with WHOPAR format	15
8.2.6	Compliance of medical information in provided PIL with WHOPAR PIL	17
8.3	Quality, readability, layout and design of the PILs	20
8.3.1	Sample eligibility	20
8.3.2	Language	20
8.3.3	Readability of the PILs	20
8.3.4	Baker Able Leaflet Design (BALD) assessment of the PILs	20
8.3.5	Ensuring Quality Information for Patients (EQIP) evaluation of PILs	21
8.4	Evaluation of the awareness, usage and perceived value of WHO PQM-website and WHOPARs among healthcare providers in the surveyed African countries	23
8.4.1	Experiences of healthcare professionals in the surveyed countries in accessing PQM-website product information (WHOPARs) and ARV product information	23
8.4.2	Awareness and use of WHOPARs	23
8.4.3	Review by healthcare providers of the quality of product information	25
8.4.4	Review by healthcare providers of the quality of PILs	25
8.4.5	Dispensing staff	25
8.5	Evaluation of acceptance levels of selected dispersible paediatric ARV products in the surveyed African countries	27
8.5.1	Healthcare providers' experience relating to acceptance levels of selected dispersible paediatric tablets in the surveyed countries	27
8.5.2	Complaints about taste, flavour, sweetness or bitterness	27

9 Discussion	28
9.1 Objectives, achievements and limitations of the study	28
9.1.1 Objectives	28
9.1.2 Strengths and limitations of methodology	28
9.2 Overall findings	29
9.3 Objective 1: Evaluation of the compliance of sampled product information with WHO norms, standards and approved PQT information	29
9.3.1 Overall compliance of collected ARV products with WHOPARs	29
9.3.2 Overall manufacturer compliance with WHOPAR or innovator information	29
9.3.3 Overall country compliance with WHOPARs	30
9.3.4 Overall product compliance with WHOPARs	30
9.3.5 Compliance of SmPC medical content with WHOPAR SmPC	30
9.3.6 Compliance of PIL medical content with WHOPAR PIL	31
9.3.7 Overall format compliance with WHOPARs and layout and design of the evaluated ARV product information	31
9.4 Objective 2: Evaluation of the readability, format, layout and design of the collected PILs	32
9.4.1 Manufacturer practice of providing a PIL	32
9.4.2 Language	32
9.4.3 Readability of the evaluated PILs	32
9.4.4 Format of the evaluated PILs	32
9.4.5 BALD criteria of the evaluated PILs	32
9.4.6 EQIP score of the evaluated PILs	32
9.5 Objective 3: Evaluation of the value of PQTm-website product information (WHOPARs) and ARV product information for healthcare providers in the surveyed African countries	33
9.5.1 Review by healthcare providers of the SmPCs of market ARV products	33
9.5.2 Review by healthcare providers of the PIL of market ARV products	33
9.6 Objective 3: Evaluation of the acceptance of selected ARV paediatric dispersible tablets in the surveyed African countries	34
9.7 Comments from surveyed countries	34
9.8 Comments from manufacturers	35
9.9 Comments from WHO	35
10 Proposals for WHO-PQTm on future improvements	37
10.1 Improvement of WHOPAR compliance	37
10.1.1 Consultation with manufacturers	37
10.1.2 Consultation with and involvement of NRAs	37
10.2 Improvement of WHOPAR awareness and usage	37
10.3 Improvements to the readability, quality of information, structure and layout of the PILs	37
10.4 Avoidance of stigmatisation	37
10.5 Product-related PI improvements	38
10.6 WHOPAR and PQTm-related recommendations	38
11 Conclusions	39
12 References	40
13 Annexes	42
13.1 Annex 1: Questionnaire WHOPAR	42
13.2 Annex 2: Questionnaire on acceptance levels of dispersible tablets	45
13.3 Annex 3: BALD scores of the evaluated 28 PILs	47
13.4 Annex 4: Individual EQIP scores of the 28 evaluated PILs	48
List of tables	49
List of figures	50

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2 Abbreviations

3TC	Lamivudine
3TC/NVP/AZT	Lamivudine/nevirapine/zidovudine
3TC/AZT	Lamivudine/zidovudine
ART	antiretroviral treatment
ARV	antiretroviral
AZT	Zidovudine
BALD	Baker Able Leaflet Design
BNF	British National Formulary
CMIT	Le Collège des Universitaires des Maladies Infectieuses et Tropicales
Disp.	dispersible
EFV	Efavirenz
EFV/FTC/TDF	Efavirenz/emtricitabine/tenofovir disoproxil fumarate
EMA	European Medicines Agency
EML	Essential Medicines List
EPAR	European Public Assessment Report
EQIP	Ensuring Quality Information for Patients
FDC	fixed-dose combination
FTC	Emtricitabine
HIV	Human Immunodeficiency Virus
IP	Intellectual Property Watch
MOH	Ministry of Health
MSF	Medicines sans Frontiers
NRA	national regulatory authority
NVP	Nevirapine
OI	opportunistic infections
PAR	public assessment report
PEPFAR	President's Emergency Plan for AIDS Relief
PI	product information
PIL	patient information leaflet
PQ	prequalified
PQT	Prequalification Unit
PQTm	Prequalification Unit - medicines assessment team
QC	quality control
RSS	Regulatory Systems Strengthening Team
SmPC	summary of product characteristics
TDF	Tenofovir disoproxil fumarate
UN	United Nations
USAID	United States Agency for International Development
US FDA	United States Food and Drug Administration
USP	US Pharmacopoeia Convention
VIH	Virus de la inmunodeficiencia humana
WHO	World Health Organization
WHOPAR	WHO public assessment report
ZNF	Zambia National Formulary
ZPCT	Zambia HIV/AIDS Prevention, Care and Treatment

3 Executive summary

This survey had two primary objectives. The first was to assess if product information (PI) supplied by manufacturers with their antiretroviral medicines to five African countries met WHO norms and standards. The second was to determine if PI supplied with sampled products met the conditions for prequalification when this status was granted by the Prequalification Unit (PQT).

This survey's secondary objectives included evaluating awareness and usage of WHO Public Assessment Reports (WHOPARs) by healthcare providers at antiretroviral treatment (ART) centres in the five African countries. This involved, inter alia, ascertaining the frequency with which healthcare providers in the field used WHOPARs and understanding their appreciation of WHOPARs' value. In addition, the survey aimed to assess the quality of presentation and format of PI supplied by medicinal product manufacturers with their products in resource-limited countries. A further objective was to ascertain if selected paediatric dispersible tablets were considered to be palatable.

WHO conducted this survey within the context of a main quality control (QC) survey of eight selected antiretroviral (ARV) products. Samples were collected between September and November 2015 at different sites (e.g. national drug stores, major dispensing facilities and ART centres) in five African countries (Burkina Faso, Democratic Republic of the Congo, Nigeria, Rwanda and Zambia). Accompanying PI for 107 prequalified and non-prequalified products was collected and analysed for its compliance with the medical content and format of published WHOPARs. Questionnaires were used for two purposes: to survey healthcare providers' overall awareness of the Prequalification Programme for medicines (PQTm)-website and WHOPARs; and to assess the quality and frequency of usage of these resources. It was possible to establish ART centre staff's general opinion of the quality of the prescribing information accompanying ARV products and the acceptance levels of dispersible ARV products for paediatrics, using a questionnaire completed by ART centre staff during interview sessions conducted by the sampling staff. Forty-nine (49) questionnaires were received and evaluated for this survey.

In total, 82% of ARV product samples included in this survey were not in line with published WHOPAR information. Only a quarter of the collected samples

were supplied with a Patient Information Leaflet (PIL). Of these, 91% did not comply with published WHOPAR PILs. Only four of the evaluated products were supplied with information that was fully compliant with published WHOPAR information on prequalified (PQ) products. There was a lack of awareness of both WHOPARs and the PQTm-website. For example, 70% of interviewed ART centre staff had no awareness of either resource. Awareness of WHOPARs was not related to usage, raising the percentage of healthcare providers who do not use WHOPARs to 88%. On a more positive note, acceptance levels of dispersible ARV products for paediatric patients were reported by ART centre staff to be high in the surveyed African countries, with complaints reported by only 30% of survey participants.

The high rate of non-compliance with published WHOPAR information indicates that PQ product information is often not used by ARV product manufacturers. Non-compliance with PQ product information may pose a direct patient health risk, e.g. if indications or dosing recommendations included with the market product differ from published WHOPAR information. The quality of information that accompanies a product is as critical as the product's other attributes for ensuring the continued quality, effectiveness or safety of the product. All non-compliant PI must therefore be viewed as potentially dangerous. Clearly, not all ARV product manufacturers are aware that PI is a component of the PQ product and that unapproved alterations could result in the loss of prequalification status. Therefore, manufacturers and national regulatory authorities (NRAs) should be made aware that compliance with WHOPAR information is directly linked to both patient safety and prequalification status.

The lack of awareness of WHOPARs and the PQTm-website among treatment staff in the surveyed African countries undermines the quality of counselling given by healthcare providers for the safe use of ARV products. Rapid action, encompassing an image campaign and the development of a PQ-App, might increase awareness of WHOPARs among treatment staff. This could improve their counselling, so having a positive impact on patient health.

To be authorized to market a product in any country, manufacturers are expected to meet national requirements in that country. Although differences in the structures and contents of PILs in different

countries could be a result of different local requirements, it was noticed that national requirements did not seem to influence products' compliance or non-compliance with WHOPAR information. It was also of major concern that none of the surveyed countries' NRAs was able to provide copies of the approved PI during the survey period. Therefore, compliance with the NRA-approved PI could not be evaluated.

None of the PILs evaluated in this survey met the Baker Able Leaflet Design (BALD) criteria for good design characteristics. The leaflets also did not achieve adequate Ensuring Quality Information for Patients (EQIP) scores. Poor readability exacerbated the already-poor quality of the PI which did not enhance the knowledge, attitude or practices of the patient towards his or her disease management. Manufacturers and NRAs should be made aware of the need to adhere to both the BALD criteria and EQIP scores and to use the right composition and format in the prescribing information.

As noted above, acceptance of dispersible ARV products for paediatric patients was very high in the

countries surveyed. However, respondents identified lack of confidence in the handling, dispensing and usage of dispersible ARV products. Further evaluation, coupled with educational training for healthcare providers, should be undertaken to improve patient counselling.

Information from this survey has led to better understanding of the awareness, usage and perceptions of the value of WHOPARs among healthcare providers in African countries. It has identified manufacturers' general practices when supplying PI, as well as the quality, readability and format of their PI. Further, it has laid bare that the medical information supplied by manufacturers with their products does not comply with WHOPAR standards.

There is a need for corrective action to improve compliance of products on the market with published WHOPAR information, especially if the products are available following recognition of, or reliance on, WHO prequalification.

4 Introduction

WHO conducted this survey within the context of a main quality control survey of eight selected antiretroviral (ARV) products circulating in five African countries - Burkina Faso, Democratic Republic of the Congo, Nigeria, Rwanda and Zambia during 2015.

The primary objectives of the survey were to assess if the product information met WHO norms and standards and conditions for WHO prequalification. The secondary objectives were to evaluate awareness and usage of WHO Public Assessment Reports (WHOPAR) by healthcare providers. In addition, the survey aimed to assess the quality of presentation and format of product information in resource-limited countries.

Accompanying product information for 107 products was collected. 82% were not in line with published WHOPAR information, only 25% were supplied with a Patient Information Leaflet (PIL) with 91% of these non-compliant with WHOPAR PILs. There was also a lack of awareness of both WHOPARs and the WHO Prequalification website.

The quality of information that accompanies a product is as critical as the product's other attributes for ensuring the continued quality, effectiveness, or safety of the product. All non-compliant PI must therefore be viewed as potentially dangerous.

There were differences in the structure and contents of PILs in different countries attributable to different local requirements.

None of the PILs evaluated in this survey met the Baker Able Leaflet Design (BALD) criteria for good design characteristics. The leaflets also did not achieve adequate Ensuring Quality Information for Patients (EQIP) scores. Poor readability exacerbated the already-poor quality of the PI which did not enhance the knowledge, attitude, or practices of the patient towards his or her disease management.

The WHO Prequalification Team, medicines group (PQTm) was established in 2001 in response to the HIV/AIDS pandemic. Its aim was to guide UN agencies and other international organizations with respect to the quality of ARV medicines, for supply to low-income countries. WHO member states requested WHO to assist procurement organisations whose quality-assurance systems were limited, by assessing the quality of low-cost generic medicines which were increasingly entering the market^[1]. In response, WHO

created a review process^[2], including assessment criteria used by regulatory agencies applying similar or more stringent requirements, to assess product safety, efficacy and quality, manufacturing and clinical study sites and PI prior to and post-prequalification. After WHO review, products meeting PQTm standards are deemed to be prequalified (PQ) and are thus eligible for procurement. It should be noted that failure to submit documentation required to be included in a WHOPAR may result in prequalification being refused.

With manufacturers' consent, the PQTm also publishes assessment report summaries of non-proprietary information (WHOPARs) for each PQ product. These WHOPARs, which are the key output of the WHO PQTm, are publicly available on its website, providing transparency and insight into the prequalification review process and the results of inspection and assessment of listed products (<https://extranet.who.int/pqweb/medicines/prequalification-reports/whopars> ^[3]). The WHOPARs are intended as a reliable resource for regulators and procurers when making regulatory or procurement decisions. They describe the assessed and accepted quality, safety and efficacy of PQ products.

The structure and format of the WHOPAR are based on the European Public Assessment Report (EPAR) as published by the European Medicines Agency^[4] but have been adapted to meet the requirements of WHO medicines prequalification. A WHOPAR consists of eight parts (Table 1).

Table 1: Structure of a WHOPAR as described on the WHO PQTm-website

Part 1	Abstract
Part 2	All accepted presentations (including photo)
Part 3	Product information for the user
Part 4	Information for the health care provider
Part 5	Labelling
Part 6	Scientific discussion
Part 7	Steps taken for prequalification
Part 8	Steps taken following prequalification.

Source: <https://extranet.who.int/pqweb/medicines/contents-and-structure-whopar> ^[5]. Last access to website: March 2022.

Parts 3 and 4 of a WHOPAR give product information for the user and the healthcare provider (<https://extranet.who.int/pqweb/medicines/contents-and-structure-whopar>^[6]). During assessment for prequalification, applicants usually submit mock-ups for initial evaluation and they are advised to submit final PI within three months of acceptance/publication of the WHOPAR. The format is expected to be in line with the recommendations by the European Medicines Agency (EMA) in the "Guideline

on the readability of the labelling and package leaflet of medicinal products for human use"^[6]. These Parts 3 and 4 are quality-assured by WHO. This information is therefore a critical component of the PQ medicinal product and its inclusion is one of the conditions for prequalification. If a product (including the PI) is altered without endorsement by the PQTm, it can no longer be considered prequalified.

5 Rationale for the survey

WHOPARs are publicly available on the PQM website (<https://extranet.who.int/pqweb/medicines/prequalification-reports/whopars>^[3]) and include information about the Summary of Product Characteristics (SmPC) and patient information leaflets (PILs). However, PI included in the packaging of products on the market sometimes differs from the PQ-approved information as published in the WHOPAR. As prequalification is not a substitute for approval by NRAs, manufacturers are expected to meet individual country requirements including labelling requirements. Manufacturers may therefore adapt PI to enable them to target several markets with a single SmPC/PIL. Until now, the impact of such manipulation on the format, completeness and accuracy of PI relative to the published WHOPAR has not been systematically evaluated. A previous WHO comparison of PI in 26 countries demonstrated

significant inter- and intra-country differences in content for specific medicines included in the survey^[7]. It is therefore essential for the PQM to verify if PQ products are supplied with appropriate information and to request manufacturers to take corrective action when necessary. In addition, the PQM needs to identify appropriate courses of action for future monitoring of PI.

Ongoing monitoring of access to its website indicates to the PQM that WHOPARs are frequently used by procurement agencies to assist in procurement decisions. However, it is not known how extensively healthcare providers in the field use or value the published information. This knowledge is essential for the PQM if it is to identify future WHOPAR improvements.

6 Scope of the survey

The survey aimed to evaluate the frequency with which healthcare providers at ART centres use WHOPARs and to understand healthcare providers' appreciation of WHOPARs' value; to assess the industry practice of providing PI in resource-limited countries, including an assessment of the quality of this information's medical content; and to analyse how well selected paediatric dispersible formulations are accepted. These evaluations were undertaken as part of a main quality control (QC) survey of a total of eight prequalified and non-qualified ARV products that were sampled between September and November 2015 in five African countries (Burkina Faso, Democratic Republic of the Congo, Nigeria, Rwanda and Zambia). The eight medicines were selected mainly because they have been procured in recent years in large quantities by international agencies such as the Global Fund to Fight AIDS, Tuberculosis and Malaria and Unitaid and were therefore expected to be widely available in the selected countries. It was considered appropriate to use the QC survey and resources to answer this survey's primary research questions and to gather additional information from the field on the use of PQ products and related aspects.

The following products were targeted:

Monocomponent medicines:

- Lamivudine (150 mg tablets),
- Efavirenz (600 mg tablets),
- Nevirapine (50 mg dispersible tablets).

Fixed-dose combinations (FDCs):

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

The inclusion of paediatric formulations in the main QC survey provided an opportunity to target medicines that had recently been prequalified.

6.1 Objectives of the survey

The primary objectives of this survey were to:

- Determine whether PI supplied with sampled products met WHO norms and standards,
- Evaluate if PI supplied with sampled products met the conditions for prequalification when this was granted by the PQTm.

The secondary objectives of this survey were to:

- Establish the value ascribed by healthcare providers in the field to information on the PQTm-website regarding PQ products,
- Review how PI is supplied with the product on the market, e.g. simply as a PIL, as a summary of product characteristics (SmPC), prescribing information only or a hybrid of these documents,
- Document issues, if any, raised by healthcare providers on acceptability (taste and palatability) of selected ARV paediatric dispersible tablets.

7 Methodology

7.1 Main activities

To evaluate objectively differences in the PI provided with the market product versus WHOPAR information, comparative checklists for the information given in the SmPCs and the PIL were prepared, following the methodology used by Reggi *et al.* [7].

To evaluate the quality of information, readability, layout and design characteristics of the collected PILs, the EQIP tool [Charvet-Berard, et al.^[8]] and BALD criteria [Adepu R and Swamy MK, 2012^[9]] were used.

The views of healthcare providers in the field on their experience of using WHOPARs and the PQM-website, as well as their awareness and perceptions of the usefulness of these resources, were evaluated for outcomes, using descriptive statistics on interview forms completed at sampling sites.

7.2 Sample collection

This survey used the sampling protocol, forms and timeline of the QC survey project. In total, 127 samples were collected in five African countries i.e. Burkina Faso, Democratic Republic of the Congo, Nigeria, Rwanda and Zambia. Samples were taken at 49 sites e.g. national drug stores, major dispensing facilities and ART centres and then secured against tampering before being sent by courier to laboratories contracted by the PQM to test product quality. After checking and confirming sample integrity and opening the packaging for testing, the PI was extracted and forwarded by the quality control laboratories to WHO for review and analysis.

7.3 Review of product information

Product information (PI) submitted with the market product was evaluated to ascertain whether:

- the format, layout and design were acceptable,
- the level of medical and pharmaceutical information was appropriate,
- accurate medical and pharmaceutical information was provided,
- comprehension was possible after simple reading.

7.3.1 Review of product information for the healthcare provider

Sections considered as most important for the safe use of the medicine were selected, based on the

variables used by Reggi *et al.*^[7] and evaluated for similarity/divergence between the sampled PI and the WHOPAR. These sections were:

- the therapeutic indications,
- dosage,
- contraindications,
- warnings and precautions,
- side effects,
- mechanism of action,
- data on clinical efficacy,
- resistance,
- absorption and bioavailability,
- distribution,
- metabolism,
- elimination,
- pharmacokinetics in special populations,
- preclinical data.

These sections were quantitatively evaluated in relation to the number of statements included in both the WHOPAR and the sampled product's prescribing information. Major deviations were quantified. Qualitative analysis and descriptive statistics were then used to show the main differences between the WHOPAR and the sampled PI. Detected deviations were categorised according to whether they were compliant or non-compliant with the WHOPAR. Further categorisation was made, based on differences between medicinal products, countries and companies.

The collected PI of products tentatively approved by the US Food and Drug Administration (US FDA), under the President's Emergency Plan for AIDS Relief (PEPFAR), was compared with the innovator prescribing information, because the US FDA-approved PI for these PEPFAR products was not publicly available. Additionally, all the other sampled products that were not prequalified at the time of this survey were compared with the innovator SmPC, following the methodological approach taken with WHO PQ products. This was done on the premise that WHOPARs are in line with the innovator SmPC in all relevant sections, i.e. indications, dosing recommendations, contraindications, warnings and precautions, drug interactions and side effects. Therefore, compliance or non-compliance of the samples with the innovator SmPC were equated to compliance with the WHOPAR.

For some fixed-dose combinations, no innovator products were available and the respective

comparison therefore could not be conducted. The respective samples, which included US FDA PEPFAR-approved products and non-prequalified products, were excluded from the analysis.

7.3.2 Review of product information for the patient

The sampled product information for the patient (or patient information) was compared with the WHOPAR PIL. The following sections considered as most important for the safe use of the medicine were selected and evaluated for similarity/divergence between the sampled patient information and the WHOPAR:

- indications (What is it and what it is used for?),
- precautions (Before you take it),
- precautions (Take special care),
- interactions (Taking with other medicines),
- dosage range (How to take it),
- possible side effects.

These sections in the patient information of WHO PQ products were compared with the relevant WHOPAR sections. Major deviations were quantified and then qualitative analysis and descriptive statistics were applied to illustrate the main differences. Detected deviations were categorised according to whether they were compliant or non-compliant with the WHOPAR. However, PK parameter deviations were categorised according to whether they were compliant, almost compliant or non-compliant. Further read-out parameters were used to show differences between, for example, medicinal products, countries or companies.

The collected patient information for products tentatively approved by US FDA (PEPFAR) was compared with the innovator PIL, because the US FDA-approved product information for the patient was not publicly available. Additionally, all sampled products that were non-prequalified at the time of this survey were compared with the innovator PIL following the same approach as that applied to WHO PQ products.

For some fixed-dose combinations, no innovator products were available. This precluded making a comparison and the products were therefore excluded from the analysis.

7.4 Evaluation of the format of the product information

The following parameters were selected to evaluate the format of the collected PI:

- Separate PI for the patient and prescribing information for healthcare providers,
- Hybrid of prescribing information and PIL,

- Totally different format including additional information e.g. "Highlights of the product information" and "Patient counselling information",
- Prescribing information for healthcare providers only,
- Product information for patients only.

The information for the 127 samples was evaluated and then shown in descriptive statistics.

7.5 Evaluation of the readability, layout and design of patient information leaflets

The evaluation of the readability, layout and design of the prescribing information was based on the European Medicines Agency (EMA) "Guideline on the readability of the labelling and package leaflet of medicinal products for human use" (ENTR/F/2/SF/jr (2009)D/869)^[6] to which WHOPAR guidance also refers. The main criteria for the evaluation of the PIL were focused on the acceptability of format, layout and design. The following reference tools were used:

1. EQIP score for assessing the quality of PIL information [Charvet-Berard *et al.*, 2008^[8]]
2. BALD criteria for format and design [Adepu R and Swamy MK, 2012^[9]]

7.5.1 Evaluation tool: EQIP Score

The EQIP score was used to assess the quality of PIL information. This evaluation tool focuses on three aspects: the content, structure and identification data of a PIL. However, in this survey, the content parameter was excluded from the EQIP score because evaluation of the medical content was done, using the EMA guide. The following 15 restructured EQIP criteria of Charvet-Berard *et al.* ^[8] were therefore used in this survey:

Identification data:

- Date of issue or revision,
- Logo of the issuing body,
- Name of persons or entities that financed the document,
- Short bibliography of evidence-based data used in the document,
- Whether the document states if and how patients were involved/consulted in its production.

Structure:

- Use of everyday language and/or complex words or jargon are explained,
- Use of generic names for all medications or products,
- Personal addresses to the reader,
- Respectful tone,
- Clear information (no ambiguities or contradictions),

- Information is balanced between risk and benefits,
- Information is presented in a logical order,
- The design and layout are satisfactory (excluding figures or graphs),
- Figures or graphs are clear and relevant (if absent, 'does not apply'),
- The document has named space for reader's notes.

Due to limited resources and the unavailability of electronic copies, PILs were not evaluated for shortness of sentences ("less than 15-word sentences") and "name of person who financed the document". Each item was coded on the four-point EQIP scales (Yes; partly; no, does not apply) in line with Moulton et al. [10]. An overall score of document quality ranging from 0 to 100% was computed according to the EQIP algorithm [Moulton et al., 2004^[10]]:

$$\text{Score \%} = \frac{\text{"yes"} \times 1 + \text{"partly"} \times 0.5}{15 - \text{"does not apply"}} \times 100$$

7.5.2 Baker Able Leaflet Design (BALD) criteria

The BALD criteria were used to assess the layout and design characteristics of the sampled PILs (Table 2). A leaflet with favourable design characteristics will improve the readability of a PIL [11],[9],[12],[13],[14],[15]. A leaflet scoring between 20 and 25 (total score 32) is considered to have good layout and design characteristics [Adepu R and Swamy M, 2012^[9]].

7.6 Evaluation questionnaire on healthcare providers' awareness, perceptions of quality and use of WHOPARs

Structured questionnaires with a limited and selected number of closed and open questions were used (Annex 1) to gather information on the general awareness, perceptions of quality and use of the PQTm-website and WHOPARs by ARV-dispensing and treatment staff. The sampling project staff arranged interview sessions with ARV treatment clinicians and pharmacist/drug-dispensing staff to answer these questionnaires. The interview outcomes were sent to WHO for further review and analysis.

Table 2: Modified Baker Able Leaflet Design (BALD) Assessment Tool

Design characteristic	3 points	2 points	1 point	0 points
Length of the line 50-89 mm long			Yes	No
Spaces between the lines	> 2.8 mm	2.2 – 2.8 mm		< 2.2 mm
Lines unjustified			Yes	No
Serif typography		Yes		No
Font Size	12 pt	10 – 11 pt	9 pt	< 9 pt
First line indented			Yes	No
Titles lowercase			Yes	No
Italics		0 words	1-3 words	≥ 4 words
Positive advice		Positive		Negative
Headings stand out		Yes		No
Numbers all Arabic			Yes	No
Boxed text			0-1 box	> 1 box
Pictograms	Words cannot replace	In between	In between	None or superfluous
Number of colours	4	3	2	1
White space	> 40%	30 – 39%	20 – 29%	< 20%
Paper quality	> 90 gsm	75 – 90 gsm		< 75 gsm

Source : Shareef *et al.*, 2016 ^[16]

Responses to the closed questions were analysed by frequency distribution and illustrated using descriptive statistics for each of the five surveyed countries. Responses to the open questions were grouped according to perceived similarities, analysed by frequency distribution and depicted using descriptive statistics.

Responses to the closed questions were analyzed by frequency distribution and illustrated by descriptive statistics. Responses to the open questions were grouped according to perceived similarities, analyzed by frequency distribution and illustrated by descriptive statistics for each country as well as for all surveyed countries.

7.7 Evaluation questionnaire on the acceptance of dispersible tablets for paediatrics

Acceptance of selected paediatric dispersible ARV formulations was evaluated using a structured questionnaire with a limited and selected number of closed and open questions to give an appropriate level of information about palatability and taste (see Annex 2). Sampling project staff arranged interview sessions with ARV treatment clinicians and pharmacist/drug-dispensing staff. The interview outcomes were sent to WHO for further review and analysis.

8 Results

8.1 Overview of the samples collected

The distribution of the 127 samples across the 49 different sites in the five African countries are depicted in Table 3. Details on sampling are available in the main report ^[17].

8.1.1 Manufacturers

The manufacturers of the 127 collected samples are shown in Table 4.

Table 3: Collected ARV drugs for this survey in the five selected countries

Products	Total numbers of samples	Countries					Distribution of samples [%]
		Burkina Faso	Democratic Republic of the Congo	Zambia	Rwanda	Nigeria	
Lamivudine 150 mg tablets	11	3	3	5	0	0	9%
Efavirenz 600 mg tablets	33	4	5	12	7	5	26%
Nevirapine 50 mg dispersible tablets	3	0	3	0	0	0	2%
3TC/NVP/AZT 30/50/60 mg disp. tablets	17	2	5	0	5	5	13%
EFV/FTC/TDF 600/200/300 mg	10	6	0	4	0	0	8%
3TC/AZT 30/60 mg dispersible tablets	14	4	2	2	6	0	11%
3TC/AZT 30/60 mg tablets	7	1	0	1	0	5	6%
3TC/AZT 150/300 mg tablets	32	5	5	11	6	5	25%
Total	127	25	23	35	24	20	
Distribution of samples [%]	100%	20%	18%	28%	19%	16%	

Table 4: Manufacturers of the sampled ARV products

Country of collection	Total number of samples	Manufacturers							
		Mylan	Cipla	Strides Arcolab	Aurobindo	Hetero Labs	Micro Labs	Macleods	Ranbaxy (Sun Pharma)
Burkina Faso	25	6	8	3	2	3	0	3	0
Democratic Republic of the Congo	23	9	1	4	3	3	2	0	1
Zambia	35	6	7	6	5	9	2	0	0
Rwanda	24	7	4	0	0	8	1	0	4
Nigeria	20	11	1	3	2	3	0	0	0
Total	127	39	21	16	12	26	5	3	5
Distribution of samples [%]	100%	31%	17%	13%	9%	20%	4%	2%	4%

To identify a potential relationship between manufacturer compliance and country compliance, manufacturers of the collected samples were depicted by country distribution. While Mylan was the major manufacturer of the sampled products in Democratic Republic of the Congo (39%) and Nigeria (55%), Hetero Labs was the main manufacturer in Rwanda (33%) and Zambia (26%). In Burkina Faso, most of the collected samples were manufactured by Cipla (32%).

8.1.2 Prequalification status of the collected samples

The prequalification status of the collected ARV products is shown in Figure 1.

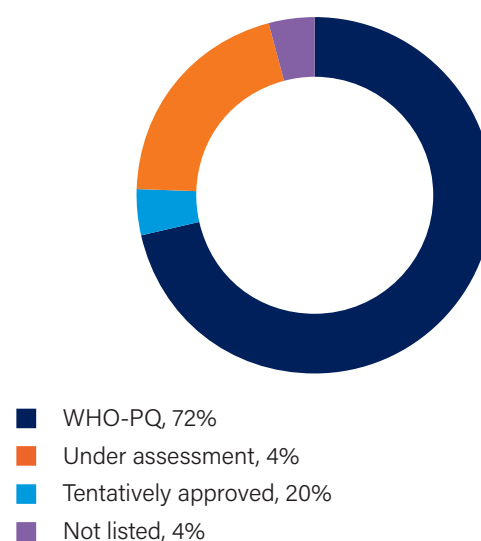
8.2 Compliance of product information with WHOPAR or Innovator PI

8.2.1 Sample eligibility

Of the 127 collected PI samples, 121 were eligible for evaluation. The other six samples were either lost post-sampling (five samples) or wrongly collected (one sample).

Of these 121 samples, 28% (36) were supplied with medicines that were not WHO prequalified. In accordance with the protocol, these samples, when possible, were compared with the innovator's PI. All 5 products (4%) from Micro Labs that were under PQTM assessment at the time of the survey were therefore compared with the innovator SmPC. The

Figure 1: Prequalification status of the collected ARV products



selection of innovators for each of the respective products was based on the current WHO comparator list^[18] (Table 5). For four products (Lamivudine/nevirapine/zidovudine 30/50/60 mg dispersible tablets, lamivudine/zidovudine 30/60 mg dispersible tablets, lamivudine/zidovudine 30/60 mg tablets and nevirapine 50 mg dispersible tablets) no originator could be identified. These are fixed-dose combinations or formulations for which no innovator product has been approved by any stringent regulatory authority.

Table 5: Innovator product list and availability of public access to PI of the products

Products	Innovator marketing authorisation holder	Innovator product name	EPAR	EPAR last revision date
3TC 150 or 300 mg tablets	ViiV Healthcare	Epivir	Yes	16.08.2016
EFV 600 mg tablets	Bristol-Myers Squibb	Sustiva	Yes	21.06.2016
NVP 50 mg disp. tablets	Not known	Not known	No	-
3TC/NVP/AZT 30/50/60 mg disp. tablets	Not known	None	No	-
EFV/FTC/TDF 600/200/300 mg	Gilead +Bristol-Myers Squibb	Atripla	Yes	13.10.2009
3TC/AZT 30/60 mg disp. tablets	Not known	Not known	No	-
3TC/AZT 30/60 mg tablets	Not known	Not known	No	-
3TC/AZT 150/300 mg tablets	ViiV Healthcare	Combivir	Yes	23.08.2016
Number of EPARs available			4	

Source: Based on the WHO comparator list^[18], EPARs were available on the EMA homepage^[19-21]. Last access to websites: March 2017.

According to the protocol, samples with no innovator and hence no available/accessible European Public Assessment Report (EPAR) were to be excluded from the analysis. An EPAR was available for only 107 samples (86%) and these were therefore eligible for evaluation. The remaining 14% of the samples could not be analyzed either because there was no public access to the PI (10%) or the samples were missing or wrongly collected (4%; see Figure 2).

8.2.2 Overall compliance with published WHOPAR information

In total, 88 (82%) of the 107 evaluated PI samples were not in line with WHOPARs, while 14% were compliant with some WHOPAR sections (Figure 2). Only four samples (4%) were fully compliant. All four were supplied by one manufacturer, Cipla, and were collected in Zambia, Democratic Republic of the Congo and Burkina Faso.

8.2.3 Overall manufacturer, country and product compliance with WHOPARs

The overall manufacturer compliance rate for the collected samples was low, as depicted in Figure 3. With 40%, Cipla was the most compliant. However, in view of the identified deficiencies of almost all samples, the value of identifying one manufacturer as the most compliant is questionable.

Figure 2: Overall compliance of the evaluated samples with WHOPARs

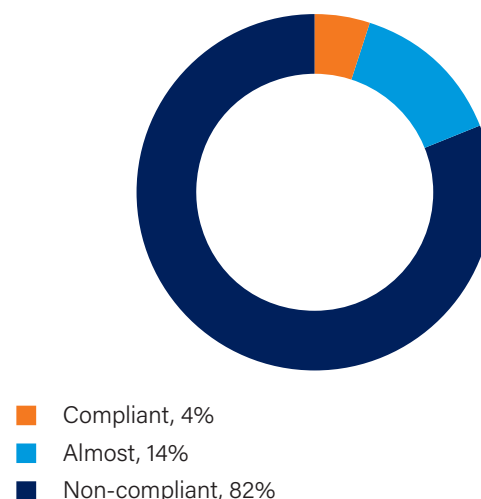
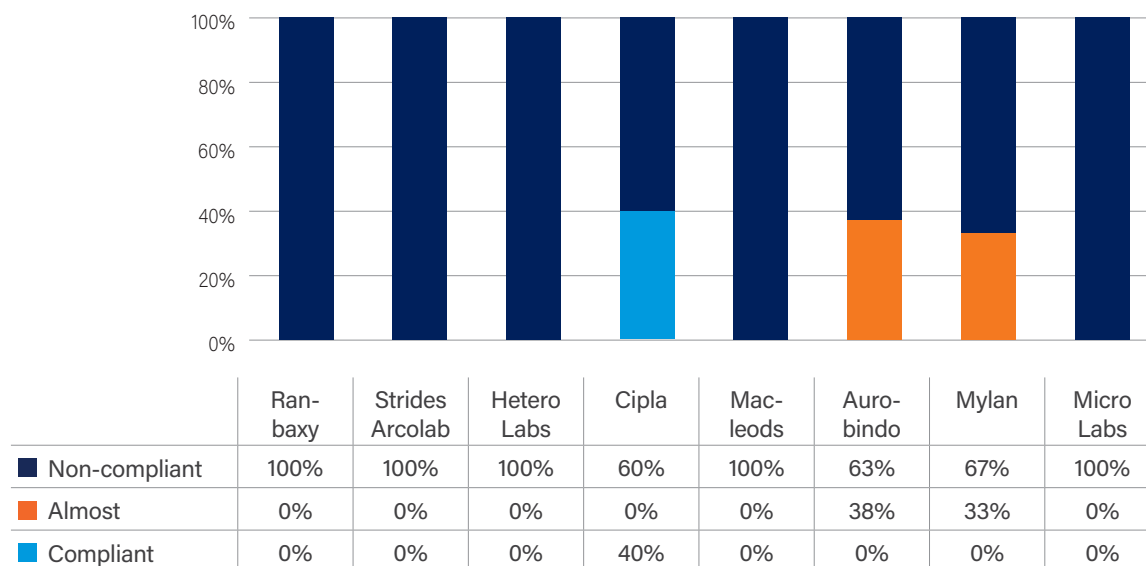


Figure 3: Overall manufacturer compliance of collected samples with WHOPARs



Similarly, the overall country compliance of the collected samples with WHOPARs was low. For Zambia, Democratic Republic of the Congo and Burkina Faso, a small percentage of PI was fully compliant (Figure 4). However, again, the identified deficiencies of almost all samples calls into question the value of highlighting one or more countries as having the most compliant PI.

The overall product compliance of the evaluated PI is shown in Figure 5. The overall compliance rate was low. However, within this context, the most compliant PI was supplied with lamivudine tablets followed by the information supplied with efavirenz tablets.

Figure 4: Overall compliance by country of the collected samples with WHOPARs

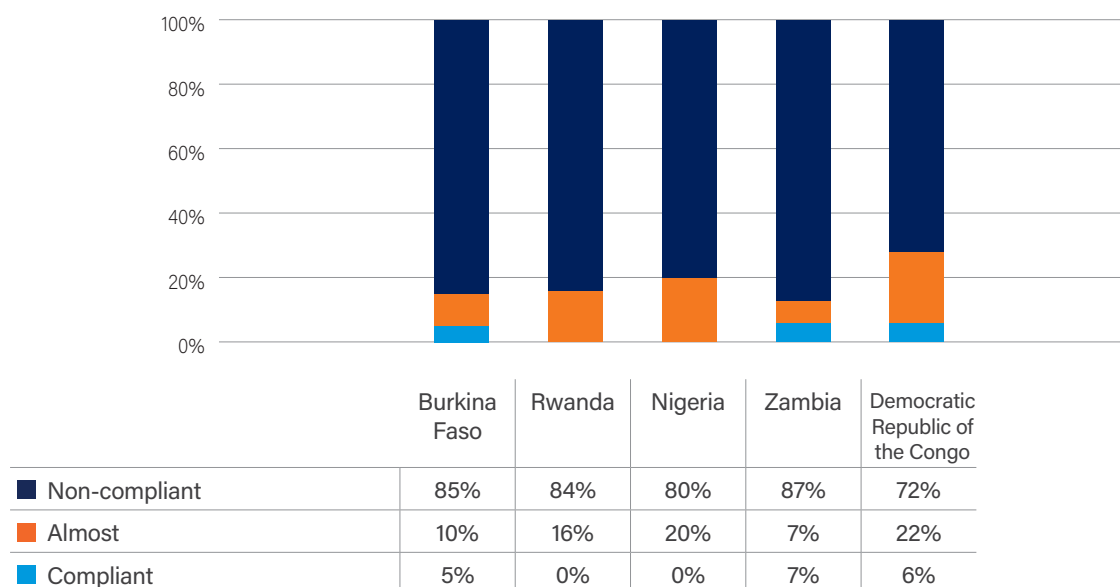
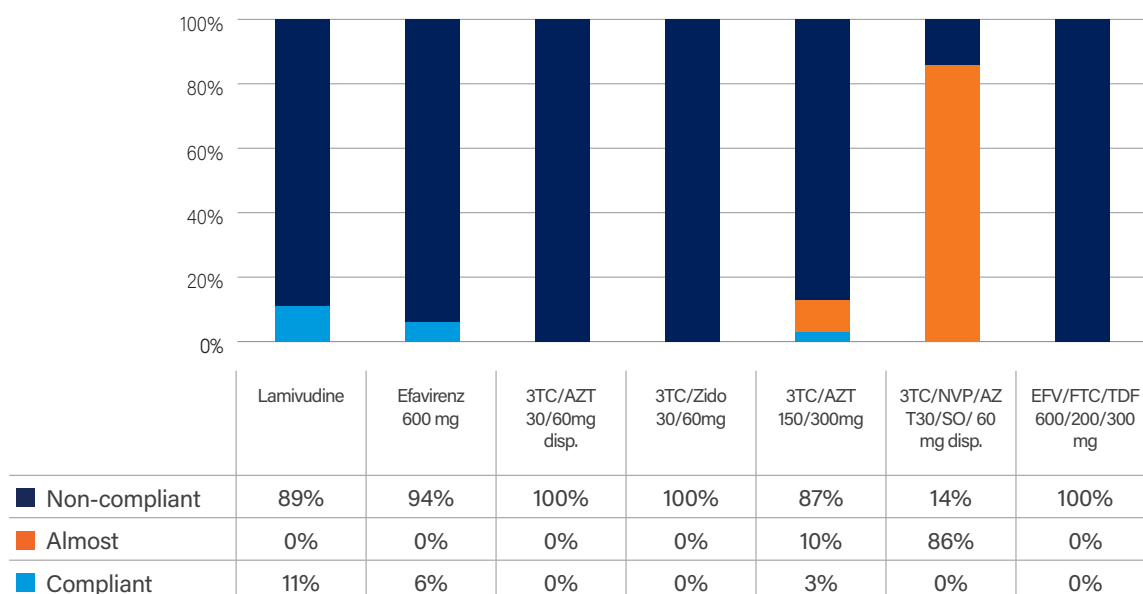


Figure 5: Overall product compliance of the collected samples with WHOPARs



8.2.4 Compliance of medical information in provided SmPCs with WHOPAR SmPCs

Of the analyzed SmPCs, 61% were not in line with WHOPARs while 24% of the samples were compliant with some sections of the WHOPAR SmPCs (Figure 6). A total of 15%, published by Cipla (35 samples) and Mylan (12 samples), were compliant.

Many of the collected samples evaluated in this survey were not in line with the WHOPAR SmPC sections concerning safe use of the medicinal product (Figure 7). Major non-compliance was noted in the therapeutic indications, dosing (posology), warnings and precautions, interactions as well as side effects. The only SmPC section that was, in most cases, compliant with the WHOPAR was the contraindications section (60%).

Figure 6: Compliance of the evaluated SmPC samples with the WHOPAR SmPCs

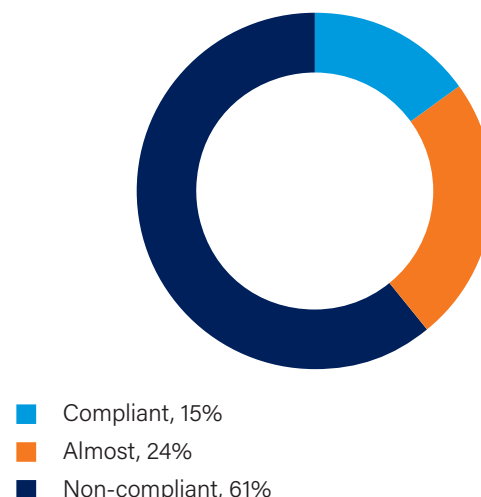
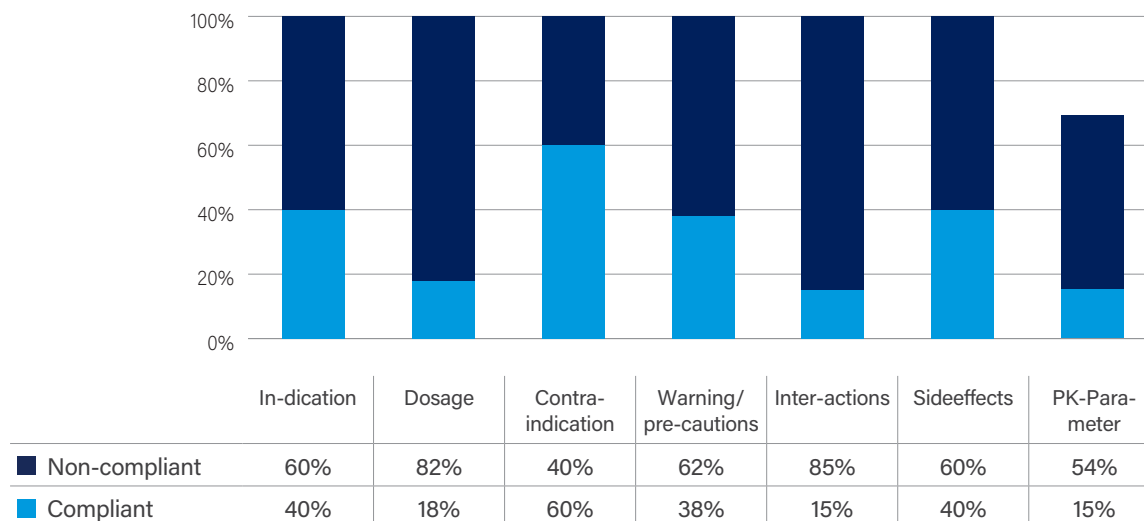


Figure 7: Compliance of the evaluated SmPC sections in the provided PI with the WHOPAR SmPC sections

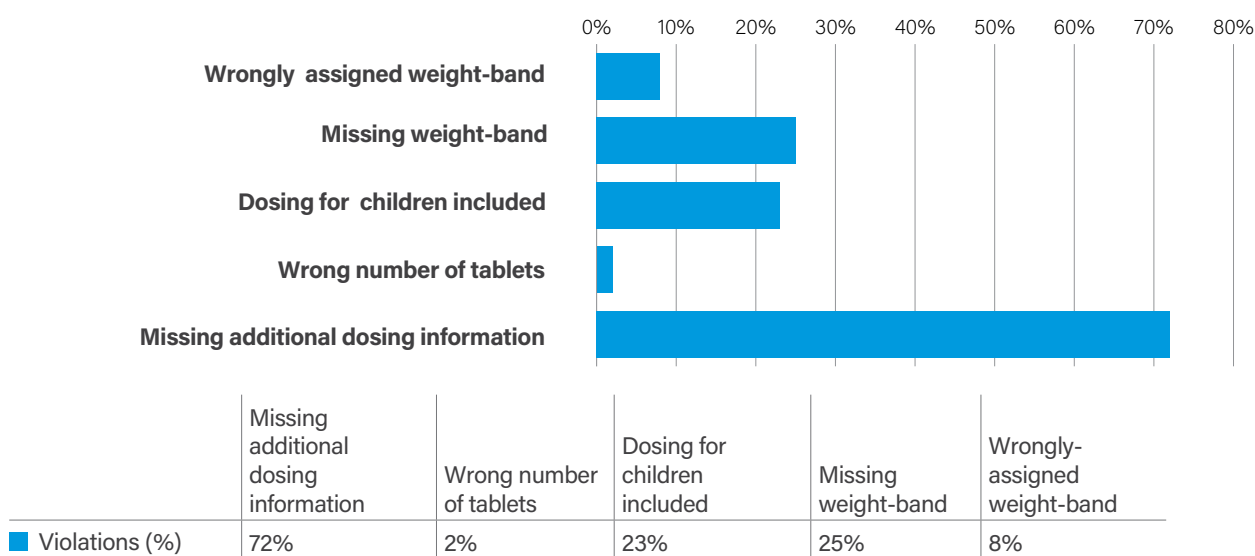


Further analysis was done to study the impact of such non-compliance on the safe use of the medicinal product. This analysis focused on dosing recommendations and the therapeutic indications. The 88 samples that included deviations in the dosing section were evaluated for serious violations which could directly impact on patient safety. In total, 80% (86 samples) of the collected samples included serious dosage violations (Figure 8). The most serious, detected in two samples, was the specification of the wrong number of tablets, resulting in a potential daily overdose of 1.5 tablets (seven-and-a-half instead of six tablets) being given to very vulnerable paediatric patients with a body weight of between 20kg and

25 kg. The inclusion of dosing recommendations for children, which were not in the WHOPAR, was identified as another serious violation.

The serious violations in dosing recommendations, depicted in Figure 8, included missing additional dosing recommendations (e.g. for renal and hepatic impairment, concomitant drug use and dose adjustments), specification of a different number of tablets to be taken daily compared with the WHOPAR, the inclusion of dosing recommendations for children, which were not in the WHOPAR, and missing or wrongly-assigned weight-based dosing recommendations compared with the WHOPAR.

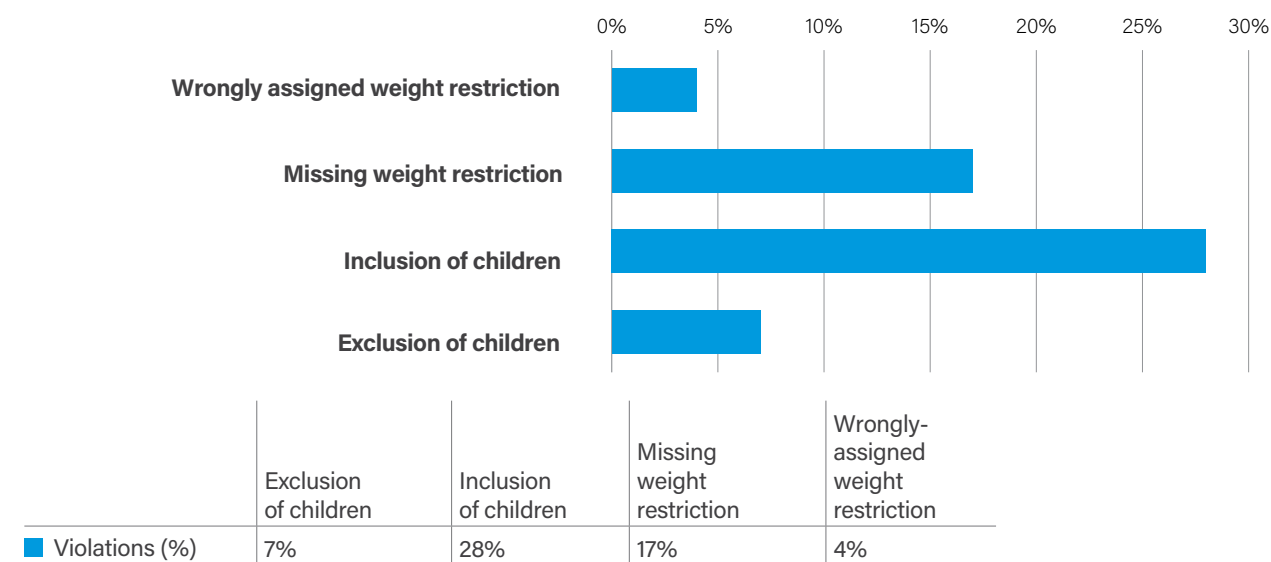
Figure 8: Serious violations regarding the dosage identified in the collected SmPCs



Of the 60% (64 samples) deviations detected in the therapeutic indications section, 54% (34 samples) were judged as serious violations (Figure 9). The inclusion or exclusion in the therapeutic indications of recommendations for product use in children and/or

adolescents, although not included or excluded in the respective WHOPARs, were in many instances judged as serious violations. Also judged as serious were alterations in, or the omission of, weight restrictions, compared with the WHOPAR.

Figure 9: Serious violations identified in the collected SmPC sections concerning the therapeutic indications



8.2.5 Collected samples' format compliance with WHOPAR format

8.2.5.1 Overall format compliance of all surveyed ARV samples

A description of the different formats used in the collected samples is provided in Figure 10. SmPCs with a "PIL-like" structure characteristically had significantly shortened sections with essential information missing. The hybrid structures, typified by the inclusion of text stating "highlights of the prescribing information" and "patient counselling information", were similar to US FDA-approved prescribing information. Of the analysed samples, 8% had a distinctly different structure from those mentioned above, with repetitive, over-long PI that included superfluous facts.

Regardless of the different identified formats, the prescribing information was evaluated in the same way. As depicted in Figure 11, the structure was clearly linked to whether one or both types of PI (for patient and/or healthcare provider) was provided with the product. Using the WHOPAR format did not correlate with inclusion of a PIL, as only 27% of this category included a PIL. None of the collected ARV products was supplied with a PIL only.

Figure 10: Distribution of different identified format structures of the evaluated samples

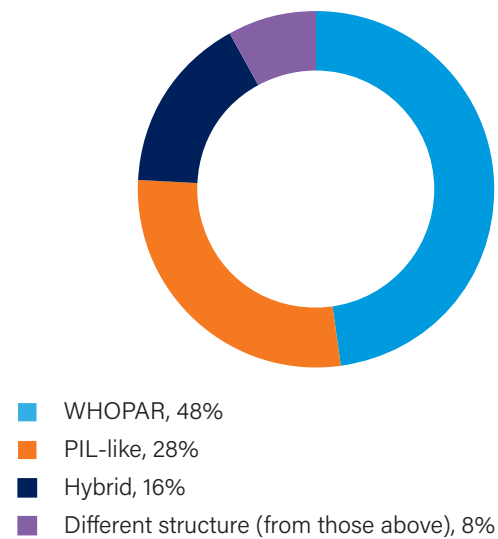
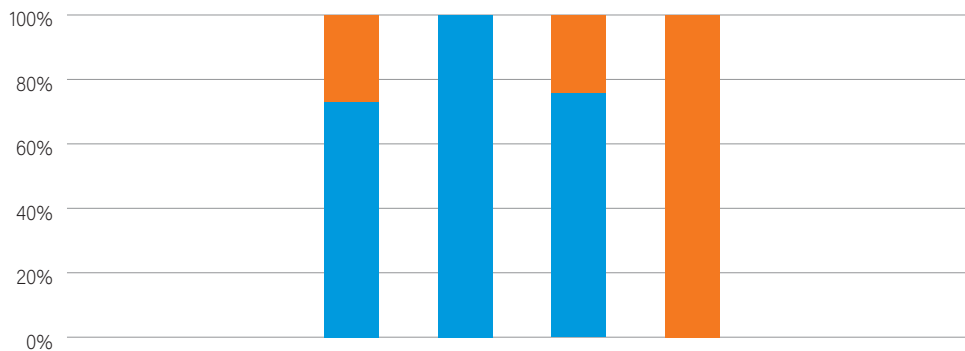


Figure 11: Included prescribing information in the evaluated product packages, in relation to the different format structures



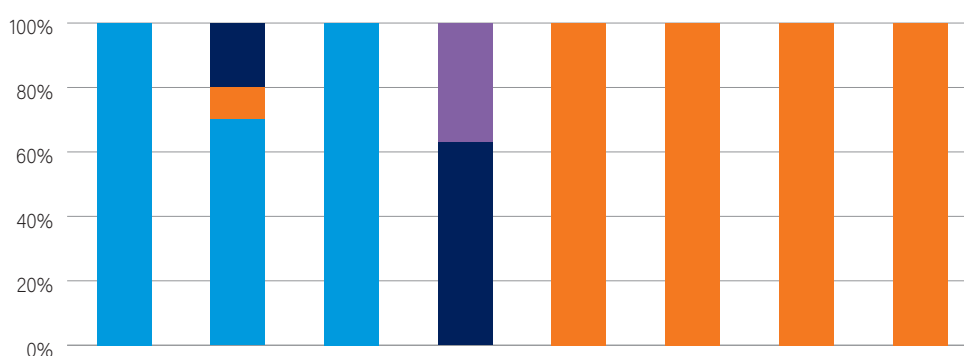
	WHO-PAR	PIL-like	Hybrid	Different structure (from those on left)
SmPC+PIL	27%	0%	24%	100%
Only SmPC	73%	100%	76%	0%

8.2.5.2 Overall format compliance of manufacturers and countries

The distribution of the different format structures among the manufacturers is depicted in Figure 12. For Mylan, all collected samples were provided with an SmPC only, which had a WHOPAR-like structure. For Cipla, 70% of the PI provided with sampled products had a WHOPAR-like structure and products were supplied with both an SmPC and a PIL. In 20% of cases, the product packs of Cipla were presented in a hybrid format. These products were also provided with both an SmPC and a PIL. One of Cipla's products had a PIL-like structure and was supplied with a

PIL only. All evaluated samples of Aurobindo were written in accordance with the WHOPAR structure and were provided with both a PIL and an SmPC. In 63% of the sampled Hetero products, there was a hybrid structure; 80% of the Hetero products were supplied with only an SmPC and 20% were provided with both an SmPC and a PIL. A total of 38% of the Hetero samples were written in a "different" format and all these samples were provided with an SmPC and a PIL. All collected samples of Strides Arcolab, Ranbaxy, Micro Labs and Macleods had a PIL-like structure and were provided with an SmPC only.

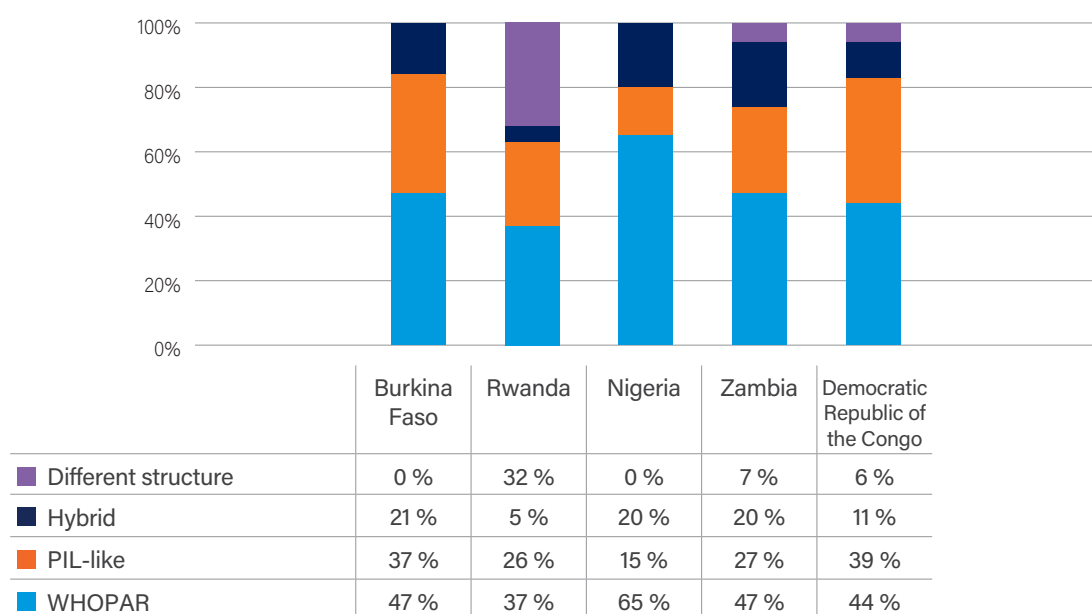
Figure 12: Distribution of the different identified format structures across the manufacturers



	Ran-baxy	Strides Arcolab	Hetero Labs	Cipla	Macleods	Aurobindo	Mylan	Micro Labs
Different structure	0 %	0 %	0 %	37 %	0 %	0 %	0 %	0 %
Hybrid	0 %	20 %	0 %	63 %	0 %	0 %	0 %	0 %
PIL-like	0 %	10 %	0 %	0 %	100 %	100 %	100 %	100 %
WHOPAR	100 %	70 %	100 %	0 %	0 %	0 %	0 %	0 %

The frequency of format distribution by country is shown in Figure 13.

Figure 13: Distribution of the different identified product information structures in the surveyed countries



8.2.5.3 BALD criteria review

8.2.5.3.1 Language

All evaluated prescribing information was provided in English and in 94% of cases, a French version was also available. In most cases, this meant that each language appeared on the reverse of the paper on which the prescribing information was written. Alternatively (mostly when the prescribing information was very long, i.e. revealing a hybrid format), two separate PILs, one in English and one in French, were available as separate pieces of paper.

8.2.5.3.2 Font size

The font or text size is the overall size (generally the height) of letters on a screen or page. A font is typically measured using point (pt) sizes which indicate the letters' vertical measurement. According to the European Commission Guideline on the readability of the labelling and package leaflet of medicinal products for human use, the font size should be as big as possible to aid the reader^[6]. Since November 2011, a font size of 9 points, as measured in an uncondensed 'Times New Roman' font, with a line-space of at least 3mm, should be considered as the minimum for package leaflets. This is because this font size is considered the minimum required for easy readability^[6]. Prior to this, font sizes of 8pt were accepted as the absolute minimum^[7]. Following visual evaluation using the BALD criteria, it was found that 24 products (23%) of the 107 evaluated for this

survey were supplied with PI that did not have text in big enough font sizes. In these cases, either the PIL, SmPC or both were written in font sizes below 8pt and this made a simple reading difficult. None of the font sizes used in the sampled PI matched the appropriate BALD-criteria (>9pt). It is essential that improvements are made.

8.2.5.3.3 Layout/size

The paper size of almost all sampled PI was too big (up to A2 format), despite the samples using font sizes that were small. Changing the length of text and its font size is one way that products which included WHOPAR-like PI could be improved. The paper sizes of PI samples with a hybrid structure were all too big, although the type's font sizes were very small. This was also the case in samples that used a different structure. All products which were provided with a PIL-like structure were generally acceptable regarding the length, size and font size of the PI. Some of the sampled PI had very faint print, an additional obstacle to good comprehension.

8.2.6 Compliance of medical information in provided PIL with WHOPAR PIL

8.2.6.1 Sample eligibility

Of the collected samples that were eligible for evaluation of the prescribing information, 86% were checked for the presence of a PIL. A total of 28 (26%) of these 107 samples included a PIL.

8.2.6.2 Overall compliance of all PILs with WHOPAR PILs

Of these 28 PILs, 91% were non-compliant with the WHOPAR PIL (Figure 14), 4% were fully compliant and 5% were compliant with only some of the selected sections evaluated for the PIL (Figure 18). The overall compliance of the collected PILs included all collected samples. Non-inclusion of a PIL in the market product was judged as non-compliance with the WHOPAR PIL.

The compliance evaluation of the sections considered as most relevant for the safe use of the product, as well as overall country, product and manufacturer compliance, was conducted for only the 28 available PILs. As depicted in Figure 15, in most cases the evaluated parameters for the PIL were not in line with WHOPAR.

Figure 14: Compliance of the evaluated PILs with WHOPAR PILs

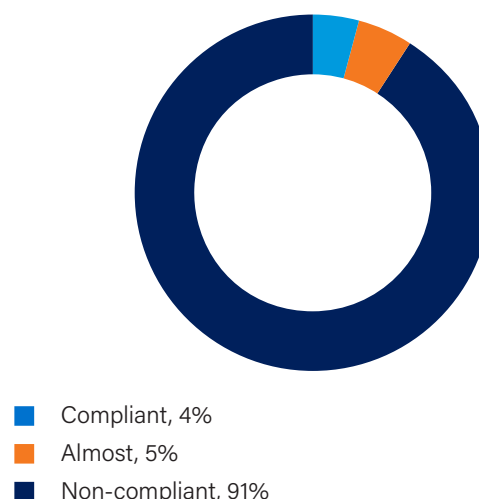
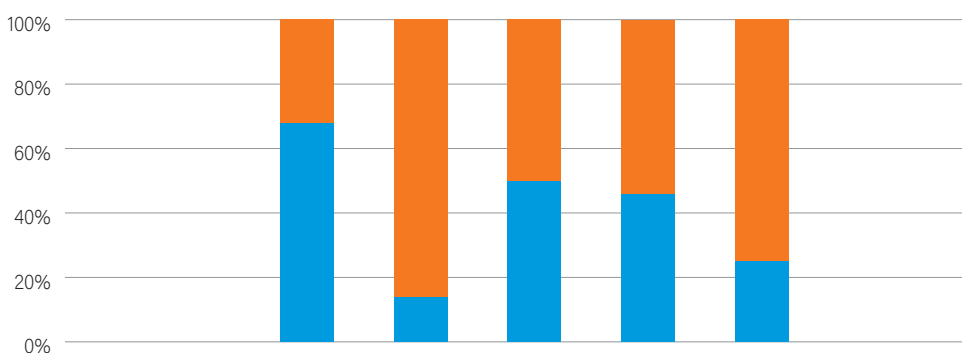


Figure 15: Compliance of evaluated PIL sections in collected samples with the respective WHOPAR PIL sections



	Indica- tion	Dosage	Contra- indication	Precau- tions	Side effects
Non-compliant	32%	86%	50%	54%	75%
Compliant	68%	14%	50%	46%	25%

8.2.6.3 Overall manufacturer, country and product compliance with WHOPAR PILs

The overall manufacturer compliance rate of the collected PILs was low, as shown in Figure 16. With 40%, Cipla was the most compliant manufacturer. However, in light of the identified deficiencies of most PILs, the value of identifying one manufacturer as most compliant is questionable.

The 28 evaluated PILs were classified into compliance status per country of sampling, as depicted in

Figure 17. The most compliant PILs were collected in Democratic Republic of the Congo, followed by Zambia.

The overall PIL compliance of the evaluated 28 samples is shown in Figure 18. As noted above, for some of the evaluated samples no PIL was available and these samples were considered non-compliant. The most compliant products evaluated were lamivudine 150 mg tablets and lamivudine/zidovudine 150/300 mg tablets.

Figure 16: Overall manufacturer compliance of collected PILs with WHOPAR PILs

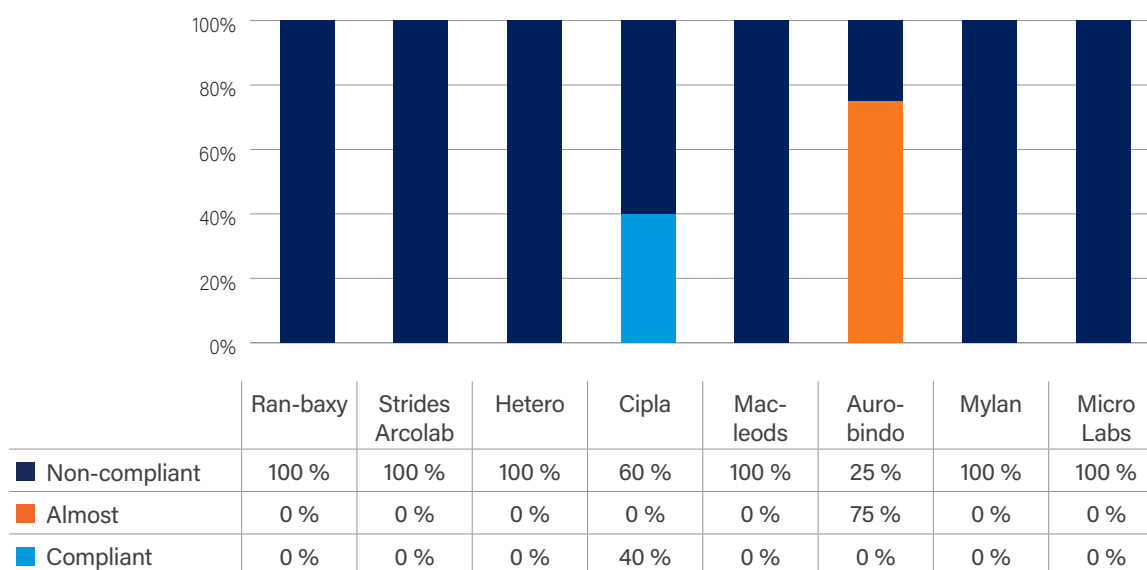


Figure 17: Overall country compliance of the evaluated 28 PILs with WHOPAR PILs

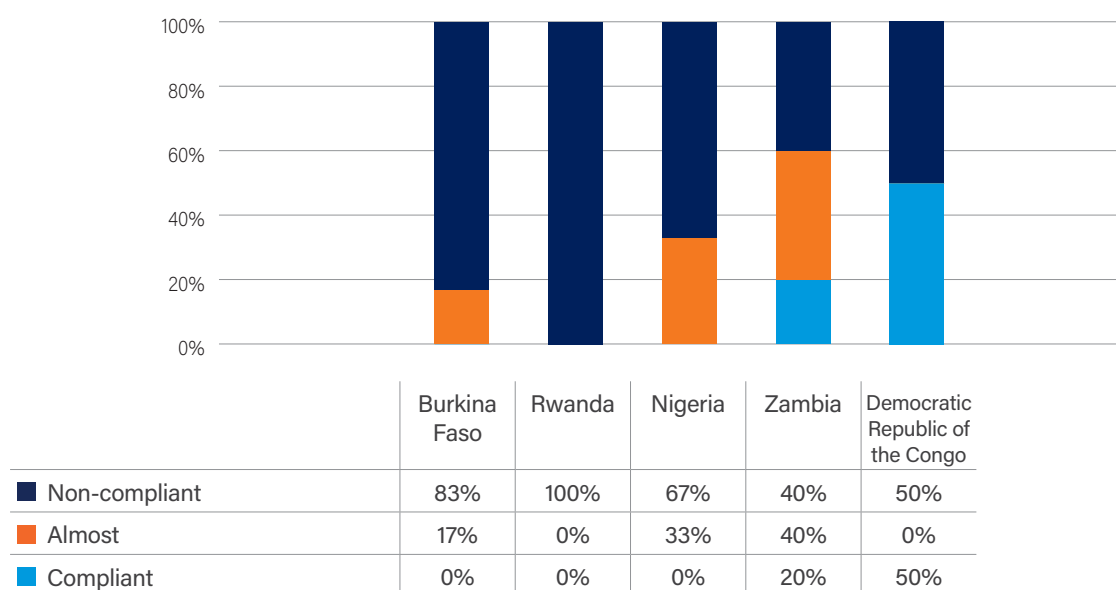
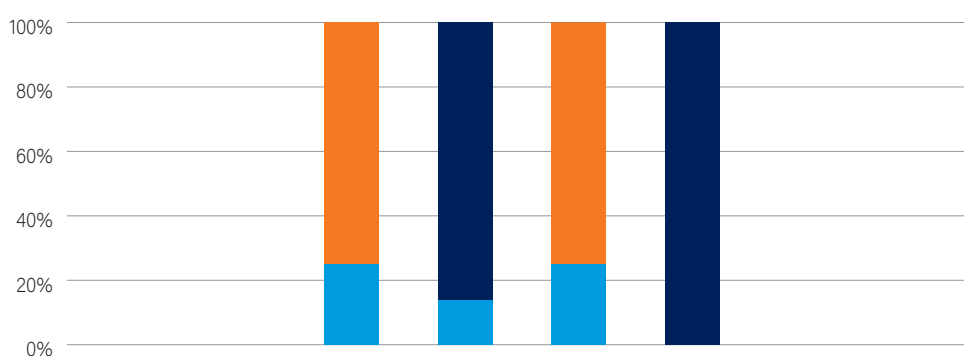


Figure 18: Product compliance of the evaluated PIL with the WHOPAR PIL



	Lamivudine 150 mg	Efavirenz 600 mg	3TC/AZT 150/300mg	EFV/FTC/TDF 600/200/300 mg
■ Non-compliant	0%	86%	0%	100%
■ Almost	75%	0%	75%	0%
■ Compliant	25%	14%	25%	0%

8.3 Quality, readability, layout and design of the PILs

8.3.1 Sample eligibility

As noted above, 28 (26%) of the 107 collected samples that were eligible for evaluation of the prescribing information included a PIL. These PILs were evaluated for their quality, readability, layout and design. The only manufacturers that provided a PIL were Cipla, Aurobindo and Hetero Labs.

8.3.2 Language

All 28 evaluated PILs were written in English and, in most cases, a French version was also available (96%). In general, this meant that the second language was on the reverse of the paper on which the prescribing information was written. In some cases (mostly when the prescribing information was very long, e.g. in the PILs provided by Hetero Labs), prescribing information in English and in French was provided, each language on separate pieces of paper.

8.3.3 Readability of the PILs

A visual check showed that 71% of PILs were unacceptable because they had font sizes smaller than 8pt. In these cases, the PILs were written in even smaller font sizes than the SmPC. Most of the PILs with non-acceptable font sizes used such small type that it was readable only with a magnifying glass. The PILs that were considered unreadable encompassed all PILs provided by both Hetero Labs (11 samples)

and Aurobindo (8 samples). A quarter of the samples had sufficient font sizes of 9pt and 4% had sufficient font sizes of 8pt. These acceptable PILs were provided by only one manufacturer, Cipla.

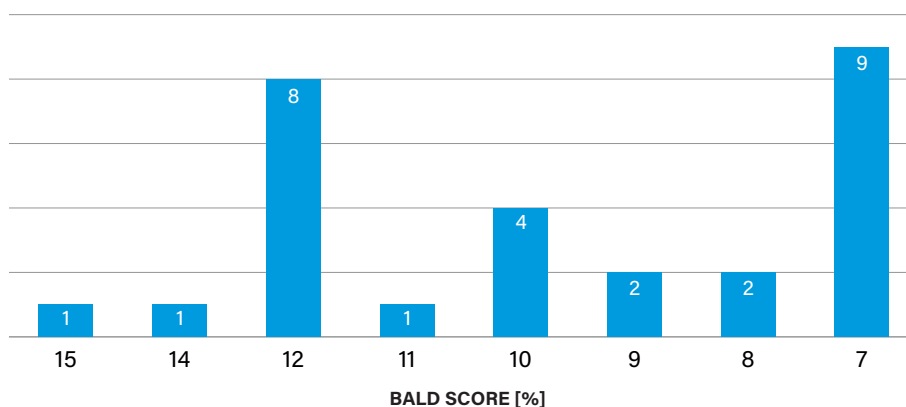
8.3.4 Baker Able Leaflet Design (BALD) assessment of the PILs

BALD criteria were applied to assess the layout and design characteristics of the 28 collected PILs. The mean BALD score of all evaluated PILs was 10% (individual PIL scores ranged between 7 and 15%). Annex 3 shows the BALD score for individual PILs.

The BALD scores of individual PILs supplied by Aurobindo and Hetero Labs were consistent for the same market product throughout the surveyed countries (see Annex 3). However, the BALD scores of the PILs for the same market product of Cipla varied within one country as well as between different countries. The highest BALD scores of 12% and lowest scores of 9% for the same product were detected in the same country while highest scores of 14% and lowest scores of 9% for the same product were identified in different countries.

Figure 19 shows the BALD score distribution of the evaluated PILs. While a leaflet scoring between 20 and 25% (maximum score is 32%) is considered to have good layout and design characteristics [Adepu *et al.*, 2012 ^[9]], the highest BALD score achieved in this survey was 15% (Cipla). Thus, none of the PILs analysed in this survey met the BALD criteria.

Figure 19: BALD score distribution of the evaluated PILs



8.3.4.1 BALD score of PILs by manufacturer and country

The mean BALD scores for the evaluated PILs by manufacturer are shown in Table 6.

Table 6: Mean BALD score of the PILs by surveyed manufacturer

Manufacturer	Mean BALD score [%]
Hetero Labs	7
Cipla	12
Aurobindo	12

The mean BALD scores for the evaluated PILs by country are depicted in Table 7.

Table 7: Mean BALD score of the PILs in the surveyed countries

Country	Mean BALD score (%)
Burkina Faso	10
Zambia	11
Nigeria	10
Rwanda	7
Democratic Republic of the Congo	10

8.3.5 Ensuring Quality Information for Patients (EQIP) evaluation of PILs

8.3.5.1 Overall EQIP score

EQIP criteria were applied to assess the quality characteristics of the 28 collected PILs, using a

scoring of document quality ranging from 0 to 100%. The overall mean EQIP score of all 28 evaluated PILs was 60%. In Annex 4 the individual EQIP score of all sampled PILs is shown. The EQIP scores of the PILs varied from 43% to 86%.

The EQIP scores of the individual PILs showed that those supplied by Aurobindo and Hetero Labs were consistent regarding their quality for the same market product throughout the surveyed countries (see Annex 4). However, the EQIP scores of the PILs for the same market product supplied by Cipla varied within one country as well as in different countries. EQIP scores ranging from 61 to 46% for one product were found in the same country while scores from 79 to 43% for the same product were identified in different countries.

Table 8 shows the mean EQIP score of the sampled PILs in the five surveyed African countries.

Table 8: Mean EQIP scores of the evaluated PILs in the surveyed countries

Country	Mean EQIP score (%)
Burkina Faso	60
Zambia	62
Nigeria	52
Democratic Republic of the Congo	66
Rwanda	57

As shown in Table 9, PILs supplied by Cipla had the highest mean EQIP score (65%), followed by those supplied by Aurobindo (58%). Hetero Labs' PILs had the lowest mean EQIP score (56%).

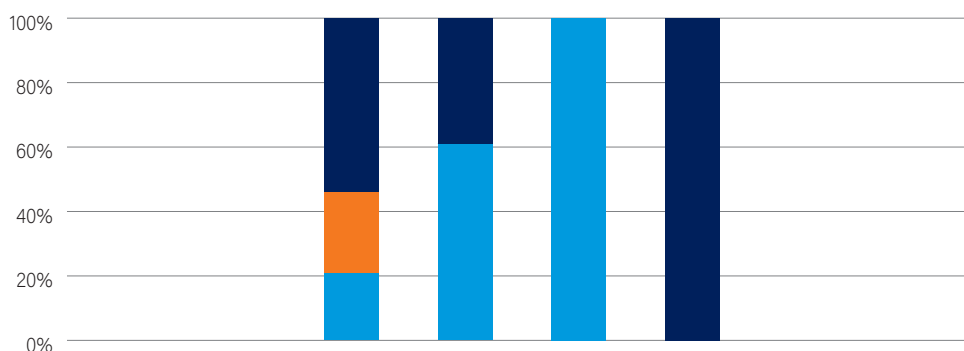
Table 9: Mean EQIP scores of the evaluated PILs for the surveyed manufacturers

Manufacturer	Mean EQIP score (%)
Hetero Labs	56
Cipla	65
Aurobindo	58

8.3.5.2 Inclusion of document identification data in the PILs

Most of the evaluated PILs were deemed to have included at least some document identification data, as depicted in Figure 20. If the last revision of the document was more than seven years ago it was considered partly compliant.

Figure 20: Evaluation of document identification data in the 28 PILs



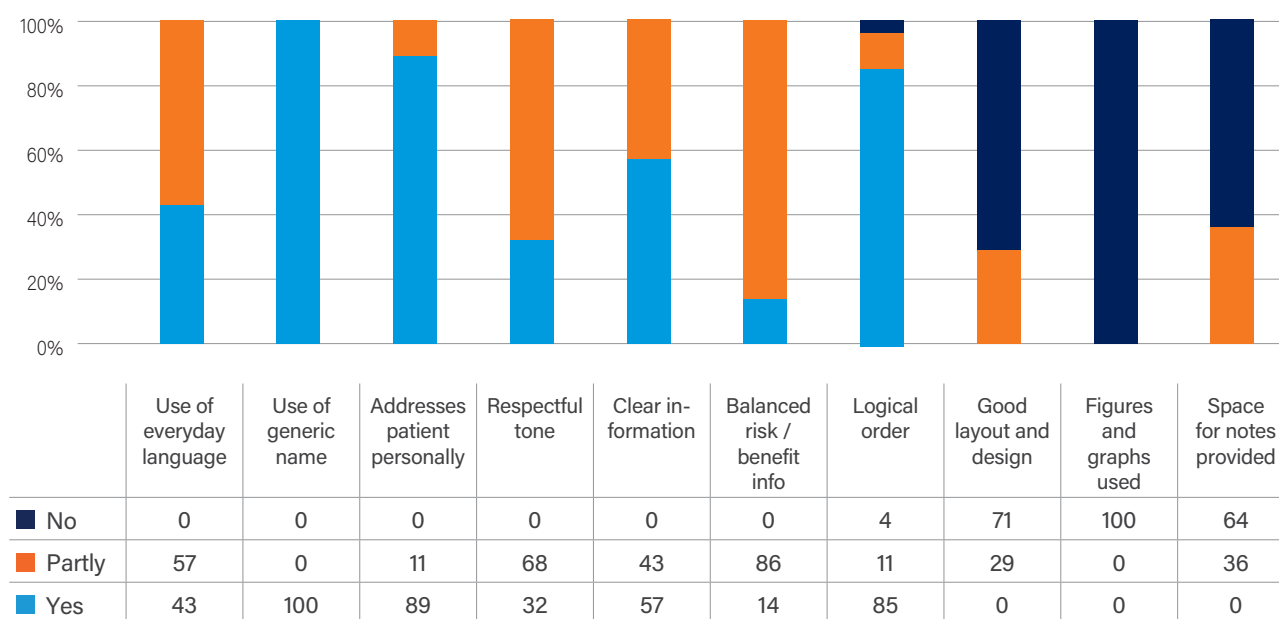
	Date of revision	Logo of manufacturer	Name of company	Patient involvement and consultation
■ No	54%	39%	0%	100%
■ Partly	25%	0%	0%	0%
■ Yes	21%	61%	100%	0%

8.3.5.3 Document structure of the PILs

The evaluation of the document structure of the 28 collected PILs is shown in Figure 21. In all cases the generic name was used for all products and medications. Most of the documents personally addressed the patient and presented the document in logical order, in line with the WHOPAR format of the PIL. In 86% of the evaluated samples, benefit-risk

information was incomplete. For example, information about interacting drugs, side effects and precautions was missing in many instances. In most cases, the design and format of the PILs were not acceptable which is a finding in line with the results of the BALD-criteria evaluation. None of the provided PILs included graphs or pictures and more than two thirds did not provide space for a reader's notes.

Figure 21: Evaluation of the document structure of the 28 evaluated PILs



8.4 Evaluation of the awareness, usage and perceived value of WHO PQM-website and WHOPARs among healthcare providers in the surveyed African countries

8.4.1 Experiences of healthcare professionals in the surveyed countries in accessing PQM-website product information (WHOPARs) and ARV product information

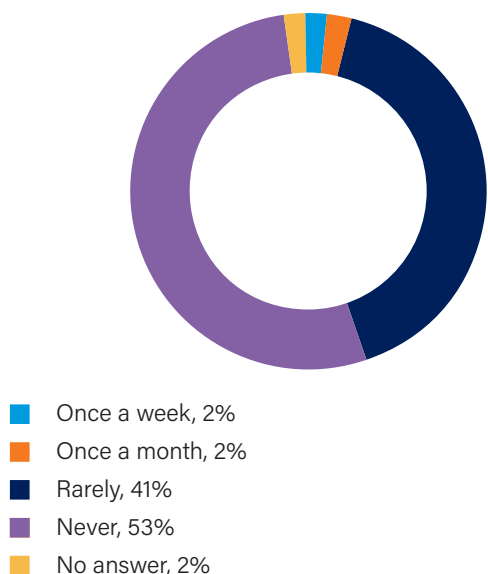
Questionnaires were used to assess the experiences of healthcare professionals in accessing WHOPARs and other information on the PQM-website. In total, 51 questionnaires were evaluated. The quality of the answers given in different countries varied and some of the questions were not clear to respondents. For example, when asked to choose a maximum of two common sources of medical information about ARVs used by ART centre staff, more answers were given in many cases. These questionnaires would normally have been excluded from the analysis as they would falsify the results of this question. However, because this mistake was made by almost all respondents, the questionnaires were included.

The composition of respondents was as follows: 47% were pharmacists or drug-dispensing staff, 45% were ART centre staff and 8% were unassigned. Fewer than half (47%) of the interviewees said they had Internet access, 49% had no access and 4% did not respond to this question.

8.4.2 Awareness and use of WHOPARs

Of the interviewed healthcare staff in the five African countries, 70% were not aware of the availability of WHOPARs, while 18% indicated they were aware of their existence but never referred to them. Only 12% stated they knew of and had referred to the WHOPARs. None of the respondents used the WHOPARs daily, while only two respondents said they referred to them either once a week or once a month (Figure 22). Nearly all respondents (96%) had no recommendation for future improvements of the WHOPARs.

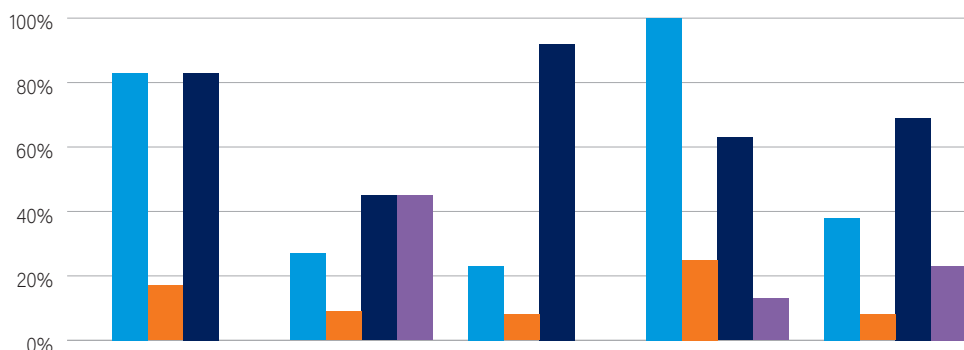
Figure 22: Frequency of use of WHOPARs and PQTm-website



The evaluation of a potential relationship between Internet access and awareness and usage of WHOPARs is shown in Figure 23.

In Rwanda and Nigeria most respondents had access to the Internet, yet awareness of WHOPARs and the PQTm-website was low (Figure 23). The lack of awareness of WHOPARs was consistently high with values between 63 and 83% in countries with high Internet access such as Rwanda and Nigeria as well as in countries with low access such as Democratic Republic of the Congo, Burkina Faso and Zambia. In countries with low Internet access, awareness of WHOPARs was between 8 and 9%. However, a higher percentage of respondents in those countries said they were aware of WHOPARs but did not use the reports.

Figure 23: Evaluation of a potential relationship between Internet access and awareness and usage of WHOPARs and the PQTm-website



	Nigeria	Democratic Republic of the Congo	Burkina Faso	Rwanda	Zambia
Internet access	83%	27%	23%	100%	38%
Know	17%	9%	8%	25%	8%
Don't know	83%	45%	92%	63%	69%
Know, but never use	0%	45%	0%	13%	23%

The most common sources of information on ART are shown in Figure 24.

Figure 24: Sources of ART information most often used by interviewees

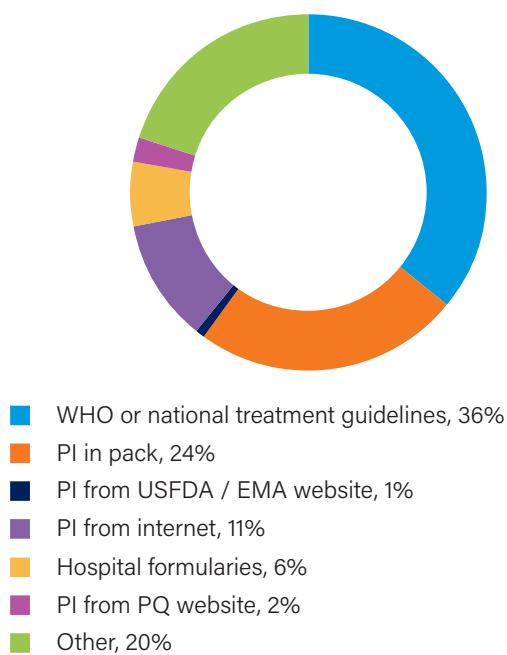
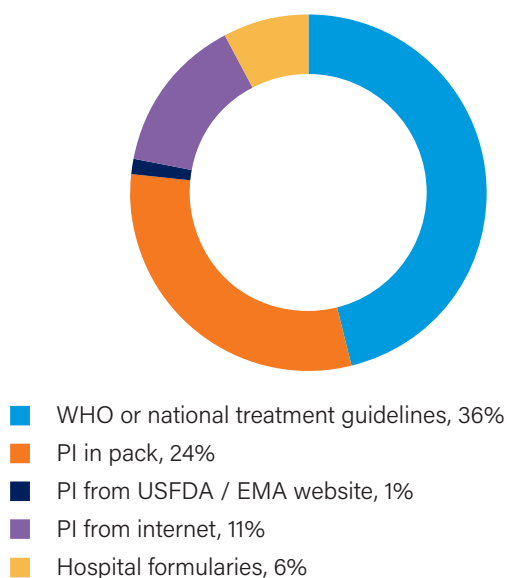


Figure 25: Respondents' evaluation of medical information in PI



Interviewees named 25 diverse sources of information on ART, including training on ART (30%), telephone conferences (20%) and NGO websites (40%).

8.4.3 Review by healthcare providers of the quality of product information

Medical information in the PI was sufficient and complete, according to 37% of interviewees (Figure 25).

Missing information was reported by 21% of respondents and 19% said they would have liked the PI to be provided in a local language. Individual participants gave a variety of other responses.

8.4.4 Review by healthcare providers of the quality of PILs

In the surveyed African countries 41% of interviewees indicated that the impact of the PIL on appropriate dosing and adherence was crucial while 37% considered it to have minimal impact. Interestingly, 15% of interviewees reported that patients left the PIL and product packs in the facility to avoid stigmatisation in their community.

A little more than a quarter (26%) of the interviewed staff stated that the PIL contained complete information and was used as the primary information source for patients; 25% said it contained reasonable information but that some patients requested additional information from the ART team; 22% responded that the PIL was of little use because it was not written in the local language (Figure 26).

Most respondents did not consider that information was omitted in the PILs. However, 4% thought dosage information was lacking and 8% thought information on interactions, side effects, contraindications and storage conditions was missing.

Interviewees' views on the shortcomings of the PILs' format and readability are depicted in Figure 27. A total of 29% did not identify any shortcomings; 16% said that the PIL was not written in the local language, used font sizes that were too small or included too much information.

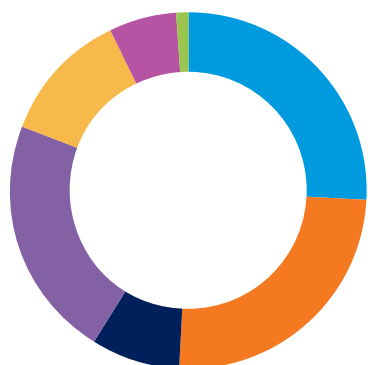
8.4.5 Dispensing staff

Nearly half (48%) of dispensing staff said the ART product package was usually supplied with only a PIL (Figure 28). Because this is not in line with the results of this survey, it raises concerns about the ability of dispensing staff to distinguish between a PIL and an SmPC.

When asked how the SmPC was supplied to healthcare providers, responses were equally distributed among the possible answers.

Compliance with the manufacturer's recommended storage conditions, as stated by dispensing staff, is depicted in Figure 29.

Figure 26: Interviewees' evaluation of the medical information in the PIL



- Complete information/primary sources, 26%
- Reasonable info but additional info requested, 25%
- Not adequate; depend on other info sources, 8%
- Little use, not written in local language, 22%
- Easily readable, 12%
- Don't use / receive it, 6%
- No answer, 1%

Figure 27: Identified shortcomings in PIL format and readability



- Not easy to read, 10%
- None / not used, 29%
- Too much information, 13%
- Small print, 13%
- No local language, 16%
- No strategy for illiteracy, 5%
- No answer, 4%

Figure 28: Interviewees' responses when asked about information supplied with ART products



- SmPC and PIL, 34%
- SmPC alone, 14%
- PIL alone, 48%
- No answer, 4%

Figure 29: Compliance with storage conditions, as reported by dispensing staff



- Always stored below 30°C, 48%
- No precaution, 31%
- No precaution despite temperatures above 30°C most days, 15%
- Exposure to temperatures above 30°C is acceptable in exceptional cases, 2%
- No answer, 4%

8.5 Evaluation of acceptance levels of selected dispersible paediatric ARV products in the surveyed African countries

8.5.1 Healthcare providers' experience relating to acceptance levels of selected dispersible paediatric tablets in the surveyed countries

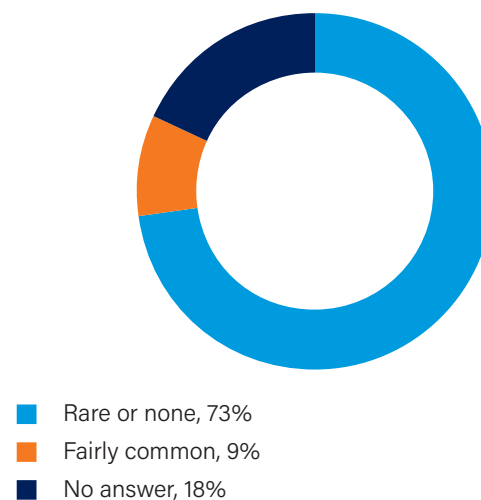
Questionnaires and interviews were used to analyze the health professionals' experience regarding the acceptance of selected dispersible paediatric tablets. A total of 47 questionnaires were evaluated. The quality of responses varied significantly from country to country. In Zambia, for example, only the first three general questions were answered and no answers were given to questions as to whether complaints had been made about the products' flavour, sweetness/bitterness or overall acceptability. For this reason, these questionnaires were excluded from the analysis. Of the interviewees, 55% were designated as pharmacists and 41% as clinicians. Most respondents (91%) indicated they considered the instructions to be easy to understand. There was, however, a difference in perception of what constituted a small amount of liquid, with 42% citing between 5ml and 10ml and 29% citing between 50ml and 100ml.

8.5.2 Complaints about taste, flavour, sweetness or bitterness

When asked about the general acceptance of the ARV products, 73% of interviewees said they rarely or never received complaints and 9% said that complaints were fairly common (Figure 30).

Three quarters of interviewees (75%) reported that they rarely or never received complaints about the flavour of dispersible tablets and a similar number (68%) reported they rarely or never received complaints about the tablets' sweetness or bitterness.

Figure 30: Frequency of complaints about dispersible tablets, as stated by interviewees



9 Discussion

9.1 Objectives, achievements and limitations of the study

9.1.1 Objectives

All objectives of the study were met. In addition to the predefined objectives, the survey produced other useful observations. These are discussed in the relevant survey objective sections.

9.1.2 Strengths and limitations of methodology

9.1.2.1 Limitations

Because of the small number of samples reviewed in the different countries for various products from different manufacturers, the results should be interpreted with caution and the possibility of chance findings borne in mind.

The study is a snapshot of the official market situation in 2015 when the samples were collected. There are therefore some important limitations on drawing general conclusions. As is often the case with surveys, these findings can be applied only to the tested samples. Extrapolation to other products not included in this survey is not necessarily valid.

The structure of the collected PI for healthcare professionals was, in most cases, a hybrid of the SmPC and PIL. Consequently, presentation of the PI was inconsistent, complicating evaluation of the prescribing information.

By designing PI criteria which were considered by the assessors to be most important for safe use of the medicines, a unique evaluation tool was created. However, the assessment as to whether missing information was important or irrelevant for the safe use of the medicine remained subjective. Although the use of multiple assessors would have given more reliable information and reduced evaluator bias, only one was used.

Review of product information for the healthcare provider

Lack of access to the PI for products tentatively approved by the US Food and Drug Administration (US FDA) under the President's Emergency Plan for AIDS Relief (PEPFAR) led to these products' collected PI being compared with the innovator prescribing information. This could have had a negative impact on the survey results, given that comparison with the PI for PEPFAR products might have shown greater compatibility.

An additional limitation to this survey's review of PI for healthcare providers is to be found in how WHOPARs were considered to be consistent with the innovator SmPC in all relevant sections. Compliance or non-compliance of the samples with the innovator SmPC were therefore equated to compliance with the WHOPAR. However, due to differential recommendations given in WHO treatment guidelines, this may not always be the case.

EQIP evaluation tool

The EQIP evaluation tool is normally used by at least two independent assessors and should be aligned with a κ -coefficient because many of the evaluated parameters are subjective. Having at least two assessors means the subjectivity can be aligned, because a confidence interval can be evaluated.

The EQIP evaluation tool was restructured for this survey by excluding the medical content. This might have implications for the EQIP score. However, Charvet-Berard *et al.* [8] restructured the EQIP tool in their study in a similar way and changed the EQIP algorithm accordingly.

Exclusion of the medical content in this survey might overestimate the EQIP scores of the sampled PILs, because of the high non-compliance of the medical content identified in the sampled PILs.

BALD criteria

The use of the BALD criteria to evaluate the layout and format of PILs did not exclude some subjectivity in, for example, defining the quality of paper used. By holding the paper, it was possible to assess its quality but not to estimate its gsm, for example. Because of time constraints, the PILs were not measured or weighed and only personal impressions of the paper's quality were used to categorise this element.

Questionnaires

The questionnaires were not tested and validated before use in the field. It was noted that in several cases, interviewees did not know how to answer questions. Repeated questions about other sources of information seemed to confuse the interviewees and this might have influenced their responses.

The questionnaires were designed to be answered in an interview session. During evaluation of the returned questionnaires, it appeared this may not have always been the case because not all questions were answered, as requested. In an interview session, the interviewer would have clarified misunderstandings.

Questionnaires not completed as required would normally be excluded from the analysis. However, because almost all the questionnaires were not fully completed, they were not excluded.

9.1.2.2 Strengths

Although an evaluator bias cannot be excluded from the assessment of the provided PI, this survey clearly demonstrated that most of the medical information provided was not in line with the published WHOPAR. This survey has therefore produced verified results, despite some evaluator subjectivity.

EQIP evaluation tool

The use of the restructured EQIP tool in this survey gave valuable results on the structure and information data of the provided PILs. Even if there was some subjectivity in the assessment, this data gives further information about the general structure and design of the evaluated samples.

BALD criteria

Most of the BALD criteria could be assessed easily by measuring or using visual, typographic evaluation methods which were not influenced by subjectivity. The results obtained, using the BALD criteria, are therefore reliable and helpful.

Questionnaires

Valuable results were obtained about the rudimentary overall awareness and use of WHOPARs by healthcare providers and dispensing staff. Information was also gained on the value of the SmPC and PIL. In addition, the survey acquired healthcare providers' recommendations for improvements in medical information. This information comes from clear statements from respondents and has not been influenced by the non-evaluated questionnaires.

Although the questionnaires' general questions about the dispersible tablets might have been considered superfluous, they gave insight into the knowledge of ART centre staff about the use of dispersible tablets. The mention of specific dispersible tablet formulations which do not exist on the market, as well as the broad interpretation of 'a small amount' of liquid, are unbiased responses which are not influenced by the non-evaluated questionnaires. They therefore gave valuable insights into the pharmaceutical knowledge of treatment staff.

9.2 Overall findings

A high rate of non-compliance with WHOPARs was identified in this survey, with only four of 107 evaluated samples being fully compliant. This high rate of non-compliance indicates that the prequalified PI is not used by manufacturers in the optimum way.

In a substantial proportion of the evaluated PI, the survey identified serious violations regarding the indications and dosing recommendations. For example, unlike in the WHOPAR, recommendations for the use in children were included in the therapeutic indications and dosing instructions were altered, independent of the provided WHOPAR. Thus, the surveyed PI's non-compliance with the prequalified PI may be directly linked to patient health risks. In view of this, all non-compliant PI must be considered to be potentially dangerous and cause for concern.

Of the interviewed ART centre staff, 70% were neither aware of the existence of WHOPARs and the PQTm-website nor used them for ARV PI or treatment considerations. This lack of awareness of WHOPAR information among healthcare providers mitigates against patients receiving high quality counselling for the safe use of ARV products.

Encouragingly, acceptance of dispersible ARV products for paediatric patients is high (70%) in the surveyed African countries. However, insecurities over the handling and dosing of dispersible tablets have been identified, which raises concerns about whether the dosing instructions were easy to understand and follow. This might have serious implications for the safe use of the medicine due to inadequate patient counselling by healthcare providers.

9.3 Objective 1: Evaluation of the compliance of sampled product information with WHO norms, standards and approved PQT information

9.3.1 Overall compliance of collected ARV products with WHOPARs

Evaluation of the overall compliance of all collected ARV products in the surveyed countries showed poor compliance with published WHOPAR information. Only four products were supplied with PI that was fully compliant.

9.3.2 Overall manufacturer compliance with WHOPAR or innovator information

Compliance of the manufacturers with published WHOPAR or innovator information was poor; the best performance at only 40% was by Cipla. Manufacturer compliance for Mylan and Aurobindo was identified at 35% and 33% respectively but applied to only the WHOPAR SmPC (Mylan) or some sections of the SmPC and PIL (Aurobindo) and not to overall compliance.

The evaluated data showed only one manufacturer with an identified relationship with compliance and this was Cipla. Aurobindo, Hetero Labs, Macleods,

Micro Labs, Mylan, Ranbaxy and Strides Arcolab were all non-compliant with their prequalified PI or respective innovator's information. The package information that was provided frequently resembled a PIL more than an SmPC. Even when headed "Prescribing information," the PI lacked most of the essential information. Different dosing recommendations were made, interactions, including information on drugs that are not recommended to be taken concomitantly, were omitted as were warnings about whole classes of interacting drugs such as antimalarials. Some warnings and precautions were omitted and sometimes side effects were incomplete or lacked detail. All aspects of the SmPC were dramatically abbreviated and some sections (e.g. resistance, clinical efficacy, preclinical data, some of the PK-data) were omitted completely. It can be concluded that safe use of medicinal products may therefore be compromised.

Manufacturers are expected to meet national requirements if their medicinal product is to receive approval in that country. One could therefore argue that the different structures and contents of prescribing information for the collected products were a consequence of different local requirements. However, it was noted that different prescribing information was provided by one manufacturer, even in the same country. Thus, national requirements do not seem to account for the products' non-compliance with WHOPARs. It also seems that NRAs do not check for compliance with WHOPARs. Of major concern was that none of the NRAs of the surveyed countries was able to provide copies of the approved PI during the survey period. Therefore, compliance with the NRA-approved PI could not be evaluated or verified.

9.3.3 Overall country compliance with WHOPARs

No real relationship between countries and compliance of the PI with WHOPARs could be established due to the limited sample size in the surveyed countries and the low compliance overall of the evaluated products.

9.3.4 Overall product compliance with WHOPARs

The product most compliant with the WHOPAR was lamivudine (150 mg tablets, 11%), followed by efavirenz (600 mg tablets, 6%) and lamivudine/zidovudine (150/300 mg tablets, 3%). None of the other evaluated products was in line with the WHOPAR.

Non-compliance was equally distributed among all collected products. Therefore, no relationship between compliance with WHOPARs and the other collected ARV products could be established. However, the limited sample size and the overall low compliance of the evaluated samples made it difficult

to establish a relationship between products and compliance with WHOPARs.

9.3.5 Compliance of SmPC medical content with WHOPAR SmPC

Evaluation of the SmPC alone identified a total of 16 SmPCs published by two manufacturers that were fully in line with published WHOPAR SmPCs. Thus, slightly better compliance of SmPCs was detected compared with the overall compliance. However, the overall non-compliance rate of the samples with WHOPARs remained significantly high.

Many of the most important sections of the assessed SmPCs were not in line with the WHOPAR sections, significantly compromising safe use of these medicinal products. The highest non-compliance rates were identified for dosing recommendations, indications and interactions, including very serious violations in dosing recommendations and indications. These have a direct impact on patient safety.

Of the identified ways that indications were non-compliant, 54% had potentially significant and serious implications for patients. In 28% of cases, unlike in the WHOPAR, products were recommended for use in children. The main concern is that an appropriate dosing of these patients cannot be achieved with the dosage strength and forms given in the relevant sections.

Additional areas in which the indications were non-compliant related to missing or wrongly-assigned weight restrictions for the target population. This may result in inappropriate concentrations of the active compound and consequently in less efficacy and the risk of developing drug resistance.

Further though relatively less significant deviations from the WHOPAR related to the omission of indications for adolescents and children. This negatively influences their treatment options in resource-limited countries.

Another potentially serious risk for patients taking ARV products was identified: dosing recommendations often differed from the PQ-approved and published WHOPAR dosage. The most serious violation was the recommendation to take the wrong number of tablets. In two specific cases for paediatric formulations, the recommended intake for a specific weight-band was 1.5 tablets per day higher than the WHOPAR recommendations. This could have serious adverse effects on vulnerable paediatric patients.

Additional deviations from the WHOPAR guideline related to the inclusion of differently-assigned or missing weight-band-dependent dosing recommendations for children, or omission of important additional dosing recommendations (e.g.

dose adjustments for renal and hepatic impairment or concomitant drugs).

Similar compliance issues were identified in the contraindications and interactions sections. Major deviations related to the omission of contraindicated or interacting drugs e.g. contraceptives, antimalarials and herbal preparations such as St. John's wort or recommendations about concomitant drug use. In addition, warnings and precautions as well as side-effects listed in the published WHOPAR SmPC were frequently missing or dramatically shortened in the sampled PIs.

This high rate of non-compliance with the WHOPAR highlights that manufacturers do not use prequalified PI in the way it is intended to be used. Further, this survey provides evidence that non-compliance of the evaluated samples with the prequalified PI may pose a patient health risk. Clearly this may have serious implications for patients and could also affect their future treatment options, particularly in resource-limited countries.

Because of this, all non-compliant PI must be considered as potentially dangerous and consequently cause for concern. Clearly, manufacturers are either not fully aware of or ignore the fact that the PI is a principal component of the conditions for prequalification of a medicinal product. Equally they seem not to know that unapproved alterations are not acceptable and may result in the loss of prequalification status. However, it should be said that this survey did not establish if all products supplied to the five countries were claiming to be WHO-prequalified. Nevertheless, there is no doubt about the need to develop a programme to improve market products' compliance with WHOPARs especially if the availability of the products is based on recognition of or reliance on WHO prequalification.

9.3.6 Compliance of PIL medical content with WHOPAR PIL

Almost three quarters of the evaluated samples were not accompanied by a PIL. Where a PIL was supplied, in most cases its quality was significantly lower than the quality of the respective SmPC information. In comparison with the WHOPAR PIL, the medical content of the sampled PILs was mostly incomplete. Sections concerning interacting drugs were dramatically shortened or missing, as in the case of contraindicated antimalarials or contraceptives. It was noted, too, that several important precautions were omitted, especially those concerning interacting drugs (e.g. St. John's wort). A comparable situation for the side effects was also noted. In contrast, the section on how to use the product was often more detailed. Concerning the indications, some PILs had a different weight-band and age range for adolescents than the

one given in the WHOPAR (e.g. 40 kg >12 years old instead of 35 kg >10 years old) and in rare instances, children and/or adolescents were included in the indications although they were not included in the WHOPAR. Based on these results, it can be concluded that the evaluated PILs did not reflect the information which was approved for the prequalified products and this might have serious implications for patients.

9.3.7 Overall format compliance with WHOPARs and layout and design of the evaluated ARV product information

The structure of most PI of the sampled WHO prequalified products was not in line with the WHOPARs. Four different format types were identified in this survey: WHOPAR format, hybrid format, PIL-like format and a different structure.

In general, most of the sampled WHOPAR-format compliant products were supplied with only an SmPC, while a small proportion included both an SmPC and PIL. There was the same breakdown for products with a hybrid structure. All samples with a PIL-like format were supplied with only a PIL, while products written in a different structure encompassed both a PIL and SmPC. None of the products was provided with a PIL only.

For products supplied with only a PIL-like structure, the counselling of the healthcare providers is inadequate and this puts patient care at risk. For products without a PIL, safe use of the medicinal product was compromised by the lack of patient-centred information. It is therefore necessary to develop interventions to ensure inclusion of all relevant PI in the market product.

All evaluated prescribing information was provided in English though in most cases, a French version was also available. Evaluation of the French version of the PI was not in the scope of this survey. In light of the relatively low literacy levels in the surveyed countries^[22], consideration should be given to translating patient information leaflets into local languages and thus increasing the probability of this information being given to the patient.

The paper size of almost all sampled PI (apart from the PIL-like structures) was too big (mostly A2 or bigger), exacerbated by a font size that was small (generally less than 9pt). All PI provided with a PIL-like structure was acceptable in terms of its word count, paper size and font size, notwithstanding the limitations noted above. Overall, however, independent of the format used, all collected samples need to be improved regarding the word count and font size used.

9.4 Objective 2: Evaluation of the readability, format, layout and design of the collected PILs

9.4.1 Manufacturer practice of providing a PIL

When PILs were provided (26% of cases), the formats were neither in line with the respective WHOPAR, nor displayed what is recommended by the EU "Guideline on the readability of the label and package leaflet of medicinal products for human use." About three quarters of manufacturers did not provide a PIL with their product. This was the case, independent of the country of distribution and the product. Cipla, Hetero Labs and Aurobindo were the only manufacturers to provide a PIL. The absence of a PIL in a market product pack mitigates against the safe use of the medicinal product. Additionally, it affects the appropriate dosing of patients and their adherence to dosing recommendations, particularly in the case of ill-informed users. Therefore, it is important to take action to ensure the inclusion of an appropriate PIL in product packs on the market.

9.4.2 Language

All sampled PILs were supplied in English and most (96%) also in French. Published literacy rates in the surveyed countries [22], suggest that many patients lack the language skills to read and understand short simple statements, regardless of the language used. However, providing the PIL in the local language, as against in English and French, would undoubtedly increase the number of patients who could read and understand the PIL.

9.4.3 Readability of the evaluated PILs

In most collected samples (71%), the font size was too small (<9pt) to permit easy reading. Although subjectivity cannot be ruled out, it was noted that a high proportion (68%) was readable only with a magnifying glass, because the font size was much smaller than 8pt. The safe use of the medicinal product could therefore be compromised, especially for patients with poor vision.

9.4.4 Format of the evaluated PILs

All provided PILs were attached to an SmPC. There were no perforations to facilitate detachment of the PIL from the SmPC. In the field, it is unlikely that drug dispensers will have access to a pair of scissors for this purpose. The inclusion of perforations may therefore improve drug dispensers' ability to provide the PIL to patients.

Frequently, patient counselling instructions were included in the prescribing information. In many of these cases, no separate patient information leaflet was provided. A variation on this practice was to

include patient counselling information in addition to the PI for the patient. This variation, which was noted in only a small number of samples, appeared to be intended as information for healthcare professionals.

The collected samples' print quality varied significantly and in some cases the print was so faint that simple reading was not possible. Sometimes the PILs were on such narrow pieces of paper that each line of text could accommodate only a few words, making reading much more difficult. In many cases, the headings and subheadings were not in bold or highlighted, making it hard to distinguish them from the rest of the text. Hence, they were of no help in finding information.

9.4.5 BALD criteria of the evaluated PILs

Internationally-accepted Baker Able Leaflet Design (BALD) criteria were used to evaluate the design characteristics of the information leaflets. Using BALD criteria, a leaflet scoring between 20 and 25% (maximum score 32%, [Adepu *et al.*, 2012^[9]]) is considered to have good layout and design characteristics [Basara *et al.*, 1994^[13]]. There was a median BALD score of 10% for all sampled products and none of them met the BALD criteria. A well-designed information leaflet with good readability, design and layout characteristics facilitates patients' understanding of its medical content. This may improve their knowledge, attitude and disease management practices [Gibbs *et al.*, 1989^[4;15]]. This survey's evaluated products made it more difficult for users to understand the medical content, as they did not reveal good design characteristics. To improve the BALD scores, manufacturers and countries should be advised to revise their documents and requirements to facilitate easier reading, more understanding and better use of PILs.

9.4.6 EQIP score of the evaluated PILs

The EQIP evaluation tool is generally used to assess the quality of information provided in the PIL. Normally, it focuses on three aspects: content, identification data and structure. The content parameter was excluded in this part of the survey because a different tool was used for this purpose. The calculated mean EQIP scores showed that the quality of information provided in the PIL was generally sufficient (60%), but there was room for improvement considering that the maximum EQIP score is 100%. According to Charvet-Berard, scores between 40 and 45% are considered to be adequate quality^[8]. However, this survey's result must be interpreted carefully since the survey modified the EQIP tool to exclude the medical content. Although it was not expected this would have implications for the survey's EQIP score, this possibility cannot be ruled out. The overall EQIP score of the evaluated

samples might be lower due to the significant deficiencies identified in the medical content of the PILs. To improve the EQIP scores, manufacturers and countries should be encouraged to improve the quality of medical information in the PIL.

9.5 Objective 3: Evaluation of the value of PQTm-website product information (WHOPARs) and ARV product information for healthcare providers in the surveyed African countries

This survey showed that the awareness, use and value of WHOPARs and the PQTm-website was very low among healthcare providers in the surveyed ART centres. Most of the interviewed ART centre staff were neither aware of, nor used, the published WHOPAR information or the PQTm-website for any information regarding ARV PI or treatment considerations. This high lack of awareness among treatment staff mitigates against patients being given high quality counselling on the safe use of ARV products. No recommendations regarding improvements of WHOPARs were received from interviewees, mainly because they did not use them. Thus, to make WHOPARs and the PQTm-website more effective, an advocacy and teaching programme in ART treatment centres may be required. This was raised by two survey participants who recommended better communication about WHOPARs and the PQTm-website.

When considering use of WHOPARs, the question of Internet access should be borne in mind: 49% of interviewees in the surveyed countries specified they did not have Internet access at their ART centre. This could account for the lack of awareness of WHOPARs. On the other hand, many people in Africa have a private mobile phone (with Internet access) which they also use for work. Therefore, lack of Internet access at ART centres may not be the only reason for low levels of awareness of WHOPARs. This caveat is supported by the fact that some respondents claimed not to have Internet access but also said they used the PI from the Internet as a source of information on ARV products.

No relationship was identified in this survey between awareness and usage of WHOPARs and Internet access. High lack of awareness of WHOPARs was found in countries with high Internet access such as Rwanda and Nigeria as well as in countries with low Internet access such as Democratic Republic of the Congo, Burkina Faso and Zambia (with values between 45 and 69% respectively). While awareness of WHOPARs was slightly higher in Nigeria and Rwanda than in countries with low Internet access,

a higher proportion of respondents in Nigeria and Rwanda also said they knew of, but did not use WHOPARs. In concluding that there is no real relationship between Internet access and awareness and usage of WHOPARs in the surveyed countries, it should be noted that the number of questionnaires received from the individual countries varied and this could have influenced interpretation of the results. The possibility of chance findings cannot be excluded.

9.5.1 Review by healthcare providers of the SmPCs of market ARV products

Most interviewees said the medical information provided in the SmPC was sufficient or appropriate. However, it should be noted that 16% of respondents claimed not to have received an SmPC with the ARV product. This would have serious implications for the safe use of ARV products since it would compromise patient counselling by ART centre healthcare providers. The PI, supplied with the product, is the most reliable form of information and should be provided to the prescribing physician. However, claims that an SmPC was not included with the ARV product could not be supported by findings in this survey, since some sort of PI for healthcare professionals was supplied in all the 107 surveyed product packs. The missing SmPCs could probably be explained by their having a PIL-like structure, which does not display all the characteristics required for an SmPC. Nevertheless, because the sample size was small, a general conclusion regarding this issue cannot be drawn.

Details of missing information were seldom given. However, NRAs need to give serious consideration to healthcare providers' recommendation that the PI should be translated into local languages to improve understanding of the prescribing information.

9.5.2 Review by healthcare providers of the PIL of market ARV products

PILs played a crucial role in ensuring appropriate dosing and adherence to treatment, according to 41% of respondents. An interesting finding of this survey was that patients in at least one surveyed country (Burkina Faso) tended to leave both the PIL and the package in the ART facility to avoid stigmatization in the community. This could have serious implications: taking the product out of the blister and transferring it to another container could expose it to the elements, e.g. light, heat and impurities. Thus, the safe use and quality of the ARV product could be compromised. Corrective action should include an information campaign to tell patients about the risks and the importance of leaving the product in its original container.

Lack of translation of the PIL into local languages, use of small font sizes, use of difficult and /or a foreign language, too much unnecessary information and the large paper format were further recognisable limitations on the usefulness of the PIL for healthcare providers. NRAs should give serious consideration to recommendations from healthcare providers about the need for better patient understanding of the PI.

Respondents' comments concerning missing information about dosing instructions, contraindications, interactions, side effects and warnings and precautions in the PI are in line with the findings of this survey. These findings highlight the urgent need for both manufacturers and NRAs to seek to improve the quality of both the SmPC and PIL that are supplied with ARV products.

Comments from the dispensing staff raised doubts about their pharmaceutical knowledge of PI and ARV product use and storage. According to them, most ARV products were supplied with a PIL only, which was at odds with the survey findings. In this survey, it was established that most ARV products were in fact not accompanied by a PIL but rather an SmPC. However, there is a correlation between the questionnaires and the survey as regards the frequency of products provided with both an SmPC and PIL. Thus, it is possible that the dispensing staff were unable to differentiate between a PIL and an SmPC.

No real conclusions could be drawn from the answers about how the SmPC was supplied to healthcare providers since replies to this question were almost equally distributed. There may be scope to study this further.

9.6 Objective 3: Evaluation of the acceptance of selected ARV paediatric dispersible tablets in the surveyed African countries

The general acceptance of the dispersible tablets in all surveyed African countries was high. Complaints regarding the taste, bitterness or other issues were rare.

However, here too, there are concerns about the pharmaceutical knowledge of the dispensing staff and, in addition, the diligence of interviewers. For example, efavirenz/lamivudine/tenofovir was reported as a dispersible formulation. As far as the assessor is aware, efavirenz/lamivudine/tenofovir has not been approved as a dispersible product.

In addition, potential insecurities regarding the handling and dosing of dispersible tablets were

identified. According to the healthcare providers, the dosing instructions were easy to read and follow at time of use. However, among respondents there was a highly variable perception of what constituted a small amount of liquid. According to the respective WHOPARs, in general a tablet should be dispensed in two teaspoons or 10 ml of drinking water. However, answering this question was complicated by the fact that the amount of drinking water required for some products was related to the number of tablets needing to be taken. Additionally, the number of tablets to be taken was related to the patient's weight. Thus, during evaluation it was difficult to distinguish between right and wrong answers. However, this variance of answers raised further concern about the clarity and appropriate compliance with the dosing instructions in market dispersible products.

Two constraints made it difficult to make recommendations about how market dispersible products should be dispensed in the surveyed countries. The first was the small number of prequalified dispersible products available for evaluation in this survey (samples of only two products made by two manufacturers were included). The second was the lack of an innovator for the non-WHO PQ products and hence the lack of EPARs for purposes of comparison. However, consideration should be given to evaluating the need for education of the dispensing staff and for more precise dosing recommendations in PI about market dispersible products.

9.7 Comments from surveyed countries

In March 2018 a review meeting with manufacturers and NRAs on the survey of PI was held in Dubai, United Arab Emirates, to discuss the outcomes and recommendations of this survey. Representatives of the NRAs from Nigeria, Rwanda and Zambia participated and comments from Democratic Republic of the Congo and Burkina Faso were submitted in writing.

There was general agreement that the deficiencies identified in the PI were not acceptable, represented a patient safety risk and needed to be corrected. The NRAs stated that the high number of applications in their countries and the number of staff currently working in the agencies made comprehensive review of PI difficult. To facilitate the revision of PI by NRAs, WHO recommended adherence to the latest published WHOPAR in the first instance. If no WHOPAR was available, the recommendations on the PQTm website and/or the innovator PI should be used as reference. NRAs noted that the PQTm could always be contacted if there were any concerns regarding the PI for prequalified products. This was, however,

on condition that the product and manufacturer were participants in the WHO collaborating process^[23]. In addition, WHO recommended signing on to the PQ mailing list to ensure receipt of the latest updates in terms of PQ (e.g. changes to WHOPARs or new products).

Delegates at the meeting said that if manufacturers sought approval of changes to PI in line with the relevant WHOPAR, they could consider expediting approval of the same if applications were submitted with evidence of PQTm approval. In addition, the NRAs were open to considering the alignment of their respective national requirements for PI with WHOPAR requirements.

Following manufacturers' highlighting of the NRAs' highly variable PI requirements which complicated their applications for approval, NRAs confirmed the need for harmonisation. Such harmonisation could begin with composition, structure, medical content, layout and design. NRAs also recognised the need to collaborate and work towards establishing reasonable timelines for the national approval of variations.

9.8 Comments from manufacturers

At the March 2018 review meeting in Dubai between WHO and NRAs, representatives from the manufacturing companies of Cipla, MacLeods, Micro Labs, Strides Arcolab and Mylan participated. Written comments were received from Aurobindo and Sun Pharma (formerly Ranbaxy).

There was consensus among manufacturers that most of the deficiencies identified in their respective PI had to be corrected. The manufacturers agreed to revise all PI with respect to the identified deficiencies in timelines mutually-agreed with the WHO PQTm. Considering that the same or similar issues could affect other products that were not evaluated in this survey, the manufacturers will also make an effort to evaluate their PI for these products with a view to taking corrective action. The initial focus would be to improve the medical content, structure, layout and design of the PI.

Manufacturers lamented the highly variable requirements and timelines for NRA review and PI approval. In addition, delays in WHOPAR publication by the PQTm, after product prequalification, could sometimes further delay the introduction of a product to some markets. A consequence of this is that manufacturers would sometimes submit and get approval of PI before publication of the WHOPAR. Hence, PI of market products could be different from the version that the PQTm eventually publishes. Seeking NRA approval after WHOPAR publication would lead to longer delays. This is why multiple

versions of PI for the same product may be available in various markets. On their part manufacturers indicated it would be possible for them to file approved new PI and variations to PI in the various countries within six months of receiving WHOPAR approval.

In order to improve PI readability, layout and design, manufacturers recommended that NRAs consider accepting products that were supplied with the PIL only i.e. without the SmPC. It was their contention that space- and print-limiting issues impeded enlarging the PI font size. Therefore, they suggested that the SmPC be made available to prescribers and caregivers by e.g. printed copies, provided by pharmacies, via websites or using scannable codes e.g. using QR codes or smartphone apps. This is already a widespread practice in many countries. Such use of e-tools could reduce the regulatory burden for manufacturers and could even allow the omission of printed registration numbers from PI. One of the participating manufacturers offered to prepare a proposal for a pilot study to be considered by WHO and the NRAs.

9.9 Comments from WHO

WHO was represented at the survey review meeting in Dubai in March 2018 by members of the PQTm and Regulatory Systems Support teams. Several recommendations and plans were made during the meeting.

To facilitate the compilation and revision of PI by manufacturers after submission, WHO recommended that manufacturers should endeavour always to adhere to the latest published WHOPAR. In cases where the product was not prequalified or a WHOPAR was not available, the innovator PI should be used. To ensure faster review of the PI by the PQTm, manufacturers were encouraged, when submitting variations, to declare sources used for compiling the PI e.g. the WHOPAR, innovator or treatment guidelines. WHO would facilitate determination of reasonable timelines for national approval of variations, after PQTm approval, and recommended that manufacturers should reciprocate by submitting approved variations to NRAs within a reasonable time.

Following recognition of the need to harmonise NRA requirements, WHO would contribute to this process by counselling the NRAs about PI requirements as well as giving guidance on the pragmatic composition, design and content of PI.

The PQTm reported ongoing initiatives to develop and publish recommended texts for products that were in the PQ lists or were showing expressions of interest.

These could then be used as templates and would facilitate the compilation of PI by the manufacturers, ensuring faster review and consistency. As an outcome of this survey, WHO was considering developing a WHOPAR/PQTm App to ensure easier access to WHOPARs.

The PQTm plans to update variation procedures to include timelines and risk categorisation of PI variations similar to other existing variations.

10 Proposals for WHO-PQTm on future improvements

10.1 Improvement of WHOPAR compliance

10.1.1 Consultation with manufacturers

The data obtained from this survey revealed that for most products, the prescribing information included in the ARV product pack was non-compliant with the PQ information as published in the WHOPAR. It is clear that manufacturers are not aware of the fact that the PI is a critical component of the conditions for prequalification of a medicinal product and that alterations are acceptable only if an application for a variation has been accepted by the PQTm. Therefore, manufacturers should be made much more aware of the importance of compliance with WHOPARs since this may have serious implications for patient safety, procurement decisions and the prequalification status of their products. They should be aware that if the PI is altered without PQTm approval, the product may no longer be considered PQ and, if put on the market claiming to be PQ, might no longer be recommended for procurement. Manufacturers should therefore be requested to take appropriate corrective action regarding the PI of the sampled products and any other PQ products they market. Additionally, manufacturers whose general practice is not to include a PIL in the product pack should be advised to do so.

10.1.2 Consultation with and involvement of NRAs

To improve compliance with WHOPARs, it is suggested that NRAs be involved in the verification of the compliance of both PQ and nationally-approved products with PQ conditions. NRAs should be made aware of how compliance with PQ product information is directly related to patient safety. WHO could benefit from this collaboration because the legal power and authority of the NRAs will facilitate follow-up action in cases of non-compliance. WHO should also consider advocacy with the NRA staff, e.g. on the composition and usage of WHOPARs and the PQTm-website.

10.2 Improvement of WHOPAR awareness and usage

Findings from this survey highlight that awareness and usage of WHOPARs and the PQTm-website is extremely low among healthcare providers in the

field. To raise the profile and increase usage of these resources, the launch of an image and education campaign is suggested. This campaign could encompass the educational training of clinicians, treatment and dispensing staff using communication materials to encourage use of WHOPARs. Advocacy on the use of the PQTm-website and WHOPARs at conferences, public health meetings, in ART treatment centres and pharmacies would also contribute to the promotion of WHOPARs. The development of a PQ Smartphone/Mobile Application (PQ-App) could be the centrepiece of this campaign. This PQ-App would be designed to give easy access to all available WHOPARs, with key-features facilitating effective patient counselling by healthcare providers in the field.

10.3 Improvements to the readability, quality of information, structure and layout of the PILs

Consulting and collaborating with manufacturers and NRAs could lead to improvements in the readability, quality of information, structure and layout of PILs. Manufacturers and NRAs could be trained on BALD criteria, EQIP evaluation and the appropriate composition and formatting of prescribing information. This should be stressed in the prequalification requirements and adopted by NRAs. In addition, consultation between manufacturers, countries and WHO regarding the translation into local languages of both prescribing information and WHOPARs is strongly recommended to improve the use and understanding of PIL.

10.4 Avoidance of stigmatisation

In Burkina Faso, patients' efforts to avoid stigmatisation were found to be a key factor of the non-usage of the PIL. Interviewed ART centre staff reported that patients leave the PIL and product pack in the treatment centre to avoid stigmatisation. As the questionnaires did not include a special question about this issue, it is not known if this is also the case in the other surveyed countries. The possibility cannot be excluded, however. Therefore, WHO should undertake an education programme about HIV, HIV

treatment and the consequences of non-treatment for infected people, especially in Burkina Faso, to alleviate the burden of stigmatisation. If the practice of leaving the PIL and product pack in ART centres is widespread, its impact on patient health may warrant further study.

10.5 Product-related PI improvements

This survey found some uncertainty about the volume of water needed for dispensing dispersible tablets. For this reason, it is recommended that all dosing recommendations of market dispersible products be reviewed. There may be a need to provide further training to help dispensing healthcare providers give appropriate instructions for administration of paediatric dispersible formulations. Manufacturers should be requested to review the PI of their market dispersible products to check the recommendations for dispensing tablets in water and if necessary, take appropriate corrective action.

10.6 WHOPAR and PQTm-related recommendations

The high non-compliance identified in this survey of PQ products may be a consequence of manufacturers' lack of compliance with the PQTm's post-qualification guidance. The innovator medicinal PI is changed over time, because of post-authorization measures and experiences, new studies that are

published, newly-authorized drugs and changing treatment recommendations. Therefore, innovators submit applications for variations to the NRAs to include relevant new information in the PI. In addition, WHO treatment guidelines, which are relevant for the PI of WHO PQ products, are updated at least every three years. For these reasons, manufacturers should align their PI with two information sources: the innovator's PI of each product (there may be more than one innovator in fixed dose combination products) and, most importantly, with current WHO treatment guidelines. The inclusion of some of these changes into the PI of a market PQ product, although not included in the WHOPAR but reflecting correct and more up-to-date medical information, might be one reason for the non-compliance of PI of some PQ products. This is entirely possible, considering that the prequalification of some products took place more than seven years ago. It should be noted that the question of whether non-compliant PI was more in line with the respective innovator SmPC was not in the scope of this survey and was not evaluated. It should also be noted that it has always been the manufacturers' responsibility to keep the PI up-to-date with respect to its regulatory and scientific contents. Mechanisms for handling these updates by the PQTm have been in place for some years (see the PQTm-website). If changes are submitted to the PQTm by the manufacturers, this leads to an update of the WHOPAR.

11 Conclusions

This survey demonstrates that it is critically important to increase usage of WHOPARs and the PQTm-website by healthcare providers at ARV treatment centres. An image campaign for WHOPARs and the PQTm-website, including educational training for healthcare providers in the field, may raise awareness and thus increase usage.

In addition, this survey's evaluation of the medical information supplied with samples of eight ARV products in five African countries shows a high rate of non-compliance with published WHOPAR information. Only four of the 107 collected samples were compliant with the PI as published in the WHOPAR. This high rate of non-compliance clearly indicates that on the market, the PQ product information is not used. Such non-compliance may pose a health risk to patients, e.g. if therapeutic indications are given that are not included in the WHOPAR or dosing recommendations are altered, independent of those provided by the WHOPAR. This is clearly worrying. Further, it seems that manufacturers are not aware that the PI is a critical component of the PQ medicinal product and that alterations to the PI without approval by the PQTm is not acceptable and might result in loss of prequalification status.

In general, most sampled products were not supplied with a PIL, i.e. a leaflet giving the characteristics of the medicinal product relevant for safe use by the patient in user-friendly language and layout. The results of this survey lead to the conclusion that medical information provided in the collected PI for patients was different from the information that, after extensive scientific evaluation, has been approved for PQ products in the respective WHOPAR PILs.

Overall, this study highlights the patient health risks of altering the format, completeness and accuracy of the published WHOPAR information in the market PI. Therefore, manufacturers should be requested to take appropriate action to correct PI supplied with their medicinal products and thus ensure their safe use. Further, manufacturers need to demonstrate adherence to conditions attached to the prequalification status of their products. In addition, NRAs are strongly encouraged to verify compliance of the nationally-approved PI with the PQ product information as this will lead to greater patient safety.

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13 Annexes

13.1 Annex 1: Questionnaire WHOPAR

Annex 4 A:

Questionnaire for 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):

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

.....

1. Most common source of medical information on ARVs for the staffs 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 USFDA/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 ARV 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 (Q 9-11)

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
i. 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 30oC"

- a. I ensure that the product is always stored at a temperature below 30oC
- b. No special precautions are exercised since the temperature in the Pharmacy is never above 30oC
- c. No special precautions are exercised even though the temperature in pharmacy in most days is above 30oC
- d. Certain excursion to a temperature above 30°C in exceptional cases is acceptable

13.2 Annex 2: Questionnaire on acceptance levels of dispersible tablets

Annex 4 B

Questionnaire for assessment of acceptability of sampled 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

13.3 Annex 3: BALD scores of the evaluated 28 PILs

Drug Substance	Sample code	Country	Manufacturer	BALD Score [%]
Lamivudine 150 mg	BF/LTV/01/091115	Burkina Faso	Aurobindo	12
Lamivudine 150 mg	ZM/LTV/016/031115	Zambia	Aurobindo	12
Lamivudine 150 mg	ZM/LTV/012/061115	Zambia	Aurobindo	12
Lamivudine 150 mg	DRC/LAT/06/271015	Democratic Republic of the Congo	Cipla	12
Efavirenz 600 mg	RW/EFV/004/20112015	Rwanda	Hetero Labs	7
Efavirenz 600 mg	RW/EFV/005/201115	Rwanda	Hetero Labs	7
Efavirenz 600 mg	RW/EFV/007/23112015	Rwanda	Hetero Labs	7
Efavirenz 600 mg	RW/EFV/006/23112015	Rwanda	Hetero Labs	7
Efavirenz 600 mg	RW/EFV/001/18112015	Rwanda	Hetero Labs	7
Efavirenz 600 mg	RW/EFV/002/18112015	Rwanda	Hetero Labs	7
Efavirenz 600 mg	ZM/EFV/008/03112015	Zambia	Hetero Labs	7
Efavirenz 600 mg	ZM/EFV/020/05112015	Zambia	Hetero Labs	7
Efavirenz 600 mg	DRC/EFV/28/101115	Democratic Republic of the Congo	Hetero Labs	7
Efavirenz 600 mg	BF/EFV/04/091115	Burkina Faso	Aurobindo	12
Efavirenz 600 mg	NG/EFV/01/090915	Nigeria	Aurobindo	12
Efavirenz 600 mg	BF/EFV/06/18112015	Burkina Faso	Cipla	11
Efavirenz 600 mg	ZM/EFV/009/061115	Zambia	Cipla	10
Efavirenz 600 mg	NG/EFV/02/090915	Nigeria	Cipla	9
3TC/AZT 150/300 mg tablets	ZM/LZT/027/06112015	Zambia	Cipla	15
3TC/AZT 150/300 mg tablets	NG/LZT/08/090915	Nigeria	Aurobindo	10
3TC/AZT 150/300 mg tablets	ZM/LZT/002/02112015	Zambia	Aurobindo	10
3TC/AZT 150/300 mg tablets	ZM/LZT/035/03112015	Zambia	Aurobindo	10
EFV/FTC/TDF 600/200/300 mg tablets	ZM/TEE/018/061115	Zambia	Cipla	12
EFV/FTC/TDF 600/200/300 mg tablets	ZM/TEE/001/021115	Zambia	Cipla	14
EFV/FTC/TDF 600/200/300 mg tablets	BF/TEE/12/09112015	Burkina Faso	Cipla	12
EFV/FTC/TDF 600/200/300 mg tablets	BF/TEE/13/12112015	Burkina Faso	Cipla	9
EFV/FTC/TDF 600/200/300 mg tablets	BF/TEE/015/171115	Burkina Faso	Hetero Labs	8
EFV/FTC/TDF 600/200/300 mg tablets	BF/TEE/010/091115	Burkina Faso	Hetero Labs	8
Mean				10

13.4 Annex 4: Individual EQIP scores of the 28 evaluated PILs

Drug substance	Sample code	Country	Manufacturer	Date of PI	EQIP score
Lamivudine 150 mg	BF/LTV/01/091115	Burkina Faso	Aurobindo	Feb 2009	61
Lamivudine 150 mg	ZM/LTV/016/031115	Zambia	Aurobindo	Feb 2009	61
Lamivudine 150 mg	ZM/LTV/012/061115	Zambia	Aurobindo	Feb 2009	61
Lamivudine 150 mg	DRC/LAT/06/271015	Democratic Republic of the Congo	Cipla	May 2011	75
Efavirenz 600 mg	RW/EFV/004/20112015	Rwanda	Hetero Labs	N/A	57
Efavirenz 600 mg	RW/EFV/005/201115	Rwanda	Hetero Labs	N/A	57
Efavirenz 600 mg	RW/EFV/007/23112015	Rwanda	Hetero Labs	N/A	57
Efavirenz 600 mg	RW/EFV/006/23112015	Rwanda	Hetero Labs	N/A	57
Efavirenz 600 mg	RW/EFV/001/18112015	Rwanda	Hetero Labs	N/A	57
Efavirenz 600 mg	RW/EFV/002/18112015	Rwanda	Hetero Labs	N/A	57
Efavirenz 600 mg	ZM/EFV/008/03112015	Zambia	Hetero Labs	N/A	57
Efavirenz 600 mg	ZM/EFV/020/05112015	Zambia	Hetero Labs	N/A	57
Efavirenz 600 mg	DRC/EFV/28/101115	Democratic Republic of the Congo	Hetero Labs	N/A	57
Efavirenz 600 mg	BF/EFV/04/091115	Burkina Faso	Aurobindo	April 2009	64
Efavirenz 600 mg	NG/EFV/01/090915	Nigeria	Aurobindo	April 2009	64
Efavirenz 600 mg	BF/EFV/06/18112015	Burkina Faso	Cipla	April 2010	79
Efavirenz 600 mg	ZM/EFV/009/061115	Zambia	Cipla	April 2010	79
Efavirenz 600 mg	NG/EFV/02/090915	Nigeria	Cipla	Nov 2011	43
3TC/AZT 150/300 mg tablets	ZM/LZT/027/06112015	Zambia	Cipla	Feb 2013	86
3TC/AZT 150/300 mg tablets	NG/LZT/08/090915	Nigeria	Aurobindo	Feb 2009	50
3TC/AZT 150/300 mg tablets	ZM/LZT/002/02112015	Zambia	Aurobindo	Feb 2009	50
3TC/AZT 150/300 mg tablets	ZM/LZT/035/03112015	Zambia	Aurobindo	Feb 2009	50
EFV/FTC/TDF 600/200/300 mg tablets	ZM/TEE/018/061115	Zambia	Cipla	Nov 2012	61
EFV/FTC/TDF 600/200/300 mg tablets	ZM/TEE/001/021115	Zambia	Cipla	Nov 2012	61
EFV/FTC/TDF 600/200/300 mg tablets	BF/TEE/12/09112015	Burkina Faso	Cipla	Nov 2012	61
EFV/FTC/TDF 600/200/300 mg tablets	BF/TEE/13/12112015	Burkina Faso	Cipla	Mar 2011	46
EFV/FTC/TDF 600/200/300 mg tablets	BF/TEE/015/171115	Burkina Faso	Hetero Labs	June 2013	54
EFV/FTC/TDF 600/200/300 mg tablets	BF/TEE/010/091115		Hetero Labs	June 2013	54
Median EQIP Score					60

List of tables

Table 1: Structure of a WHOPAR as described on the WHO PQTm-website	10
Table 2: Modified Baker Able Leaflet Design (BALD) Assessment Tool	15
Table 3: Collected ARV drugs for this survey in the five selected countries	17
Table 4: Manufacturers of the sampled ARV products	17
Table 5: Innovator product list and availability of public access to PI of the products	18
Table 6: Mean BALD score of the PILs by surveyed manufacturer	29
Table 7: Mean BALD score of the PILs in the surveyed countries	29
Table 8: Mean EQIP scores of the evaluated PILs in the surveyed countries	29
Table 9: Mean EQIP scores of the evaluated PILs for the surveyed manufacturers	30

List of figures

Figure 1: Prequalification status of the collected ARV products	18
Figure 2: Overall compliance of the evaluated samples with WHOPARs	19
Figure 3: Overall manufacturer compliance of collected samples with WHOPARs	19
Figure 4: Overall compliance by country of the collected samples with WHOPARs	20
Figure 5: Overall product compliance of the collected samples with WHOPARs	20
Figure 6: Compliance of the evaluated SmPC samples with the WHOPAR SmPCs	21
Figure 7: Compliance of the evaluated SmPC sections in the provided PI with the WHOPAR SmPC sections	21
Figure 8: Serious violations regarding the dosage identified in the collected SmPCs	22
Figure 9: Serious violations identified in the collected SmPC sections concerning the therapeutic indications	22
Figure 10: Distribution of different identified format structures of the evaluated samples	23
Figure 11: Included prescribing information in the evaluated product packages, in relation to the different format structures	23
Figure 12: Distribution of the different identified format structures across the manufacturers	24
Figure 13: Distribution of the different identified product information structures in the surveyed countries	25
Figure 14: Compliance of the evaluated PILs with WHOPAR PILs	26
Figure 15: Compliance of evaluated PIL sections in collected samples with the respective WHOPAR PIL sections	26
Figure 16: Overall manufacturer compliance of collected PILs with WHOPAR PILs	27
Figure 17: Overall country compliance of the evaluated 28 PILs with WHOPAR PILs	27
Figure 18: Product compliance of the evaluated PIL with the WHOPAR PIL	27
Figure 19: BALD score distribution of the evaluated PILs	29
Figure 21: Evaluation of the document structure of the 28 evaluated PILs	31
Figure 22: Frequency of use of WHOPARs and PQTm-website	32
Figure 23: Evaluation of a potential relationship between Internet access and awareness and usage of WHOPARs and the PQTm-website	32
Figure 24: Sources of ART information most often used by interviewees	33
Figure 25: Respondents' evaluation of medical information in PI	33
Figure 26: Interviewees' evaluation of the medical information in the PIL	34
Figure 27: Identified shortcomings in PIL format and readability	34
Figure 28: Interviewees' responses when asked about information supplied with ART products	34
Figure 29: Compliance with storage conditions, as reported by dispensing staff	34
Figure 30: Frequency of complaints about dispersible tablets, as stated by interviewees	35

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