9-2022

Regulatory Compliance of Labels and Product Information Leaflets for Medicines Distributed in the Private Sector in South Sudan

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ABSTRACT

Patient information leaflets (PILs) and labels are important for rational use of medicines as they provide additional information for patients on the medicines dispensed to them. In developing countries, this potential cannot be fully harnessed unless manufacturers provide medicines with labels and PILs that meet regulatory standards for content and user-friendliness. In South Sudan, it is not known if manufacturers uphold standards of these labels and PILs once their products are approved for distribution in the country.

This study explored the degree to which medicines distributed in South Sudan comply with regulatory requirements for labels and PILs. A cross-sectional survey was conducted at selected pharmacies in Juba, the capital city of South Sudan. Labels and PILs from tracer medicines (based on the WHO priority list of medicines for children and women) were retrieved and assessed for compliance with regulatory requirements. Clients leaving the pharmacies were also interviewed about their prescriptions and understanding of the PILs.

This study demonstrated that availability of essential medicines for maternal and child health is limited in the private sector is limited (66% overall). Furthermore, the availability and quality of labels and PILs leave a lot to be desired (79% complied with labeling requirements; 68% complied for PIL. There was a tendency for compliance of products from certain countries to be particularly poor. PILs were given out for only 38% of medicines dispensed. Most patients (92%) leaving the pharmacy did not know contraindications for the medicines dispensed, while majority (83%) had no idea what they should do if they had forgotten to take their medicine on time.

Limited availability of essential medicines in the private sector has implications on universal health coverage, as a good proportion of patients seek health care services through the private sector. Labels and PILs are essential for education on their medication and impact on rational use of medicines. Moving forward, the regulatory authority in South Sudan would benefit from establishing and implementing strict guidelines that compel importers to adhere to licensing conditions related to labels and PILs up to the last mile of the supply chain. Frequent post-marketing authorization inspections should be used to check on these aspects with punitive measures taken against non-compliant distributors.

KEYWORDS

Medicine labels, patient information leaflets (PIL), medication errors, patient safety, regulatory compliance, rational use of medicines.

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1. INTRODUCTION

For a patient to benefit from medicine given to him or her, it is important that he or she knows what it is, why it is prescribed, how it will work, what side effects to expect, and what to do in case those side effects occur. However, with increasing patient load, doctors and dispensing staff may not have enough time to counsel patients properly on the medicines prescribed. Appropriate labels and patient information leaflets (PILs) are therefore useful resources that can fill the gap in patient education to promote rational use of medicines, thereby promoting patient safety.

The PIL, as a form of written medication information, is the most easily available, accessible, and important material to provide to patients. Written medication information is important to patients as it supports, complements, and reinforces the verbal education received at counseling, and can be kept for ongoing reference (Mai & Aslani, 2007). Stichele (2004) who reviewed Belgian patient information leaflets, noted the vast majority of patients read them, and concluded the leaflets have a positive impact on patient satisfaction, regardless of their quality. This could be because patients typically wish to know more about a medicine's indication, expected benefits, duration of therapy, and an accurate list of potential adverse effects (Jeetu & Girish, 2010).

Kenny et al. (1998) reviewed use of PILs, and concluded that they can improve health outcomes because, if used well, they can bridge the information gap identified between patient-physician relationships. PILs are needed and demanded by patients. Nathan et al. (2007) surveyed a total of 307 patients in their study and found that for new medications, patients reported reading the leaflets always (49%), often (21.2%), seldom (16.0%), or never (13.7%). For refilled medications, respondents reported reading the leaflets always (21.6%), often (13.9%), seldom (26.4%), or never (38.2%). When assessed for understandability, 267 (56.2%) of those who responded reported the PIL was very easy to understand, 34.5% reported somewhat easy, 8.5% reported somewhat difficult, and 0.8% reported very difficult to understand; 63.8% reported that the PIL was useful, 35.0% reported somewhat useful, and 1.2% reported that the leaflet was not useful. They therefore recommended pharmacists should encourage reading the leaflet and promote it as a useful resource.

Despite evidence in support of use of PIL, a study conducted in Jos city, Nigeria (Ogaji et al., 2013) found that manufacturers of pharmaceuticals in Nigeria were aware of the importance of the PILs in promoting the safe and efficacious use of their medicines. However, only few of them applied this knowledge to the benefit of the users of their products. A similar study in Abu Dhabi (Gharibyar et al., 2013) found that information relevant to the safe and appropriate use of medications was not uniformly mentioned in the PILs analyzed. Additionally, of the 41 drug products obtained from online pharmacies from 12 different countries, only one product met both labeling and PIL guidelines for the United States (Veronin, 2011).

Written medication information is important to patients as it supports, complements, and reinforces the verbal education received at counseling, and can be kept for ongoing reference (Mai & Aslani, 2007). Correct and clear labeling is important because thousands of medication name pairs might be confused or have been identified as having the potential for confusion, based on similar appearances or sounds when written or spoken (Berman, 2004). Shrank et al., (2007) asserted that variability in drug labeling and the use of difficult terminology can adversely affect a patient's understanding of medication instructions. In an Australian study (Pit et al., 2008) amongst elderly people living in the community, 9% reported problems reading labels, 9% reported difficulty remembering to take the medicine, 8% did not know what the medicine was prescribed for, 6% had trouble understanding the label, and 10% had difficulty opening the bottle or packaging.

Van Dooren et al (2015) carried out an online survey with a panel of 785 Dutch pharmacy technicians and discovered patients mostly asked questions related to drug actions, problems with use, side effects, intolerances, and pregnancy and lactation. This was attributed to the PILs not providing enough information on these issues, or the patients not finding the PIL easy to read, understand, or recall. In another study, Shivkar (2009) further found that although warnings and precautions were included in a majority of PILs, they rarely mentioned information regarding pediatric use (43.8% of PILs), geriatric use (12.5% of PILs), or use in special conditions, such as liver, renal, cardiac, and other relevant conditions (38.8% of PILs).

This problem is not unique to generics. Gharibyar et al (2013) reviewed 67 PILs for branded (72%) and generic (28%) prescription-only medicines from different countries (USA, UAE, Sweden, France, UK, Japan, Germany, Canada, and Belgium) that were distributed in the Emirate of Abu Dhabi. The study demonstrates that of the PILs analyzed, only 35 (52.2%) out 67 contain clinically relevant information that was required by the Ministry of Health, while 32

(47.8%) failed in one or more of the 14 parameters evaluated.

It is therefore apparent it is uncommon to find complete lack of, or variability in, quality of packaging information inserts and product labeling that may negatively affect patient access to vital information. Several factors may be responsible, such as weak manufacturers' quality assurance system to ensure consistent compliance with marketing authorization requirements, poor regulatory oversight to detect, investigate, and sanction omissions, or various factors in the supply chain (e.g., illegal importation, sourcing from unlicensed distributors, counterfeiting, etc.).

Figure 1 below illustrates the general context and responsibilities to ensure good flow of medicine information, including accompanying labels and PILs, from manufacturers to the ultimate user (patient).

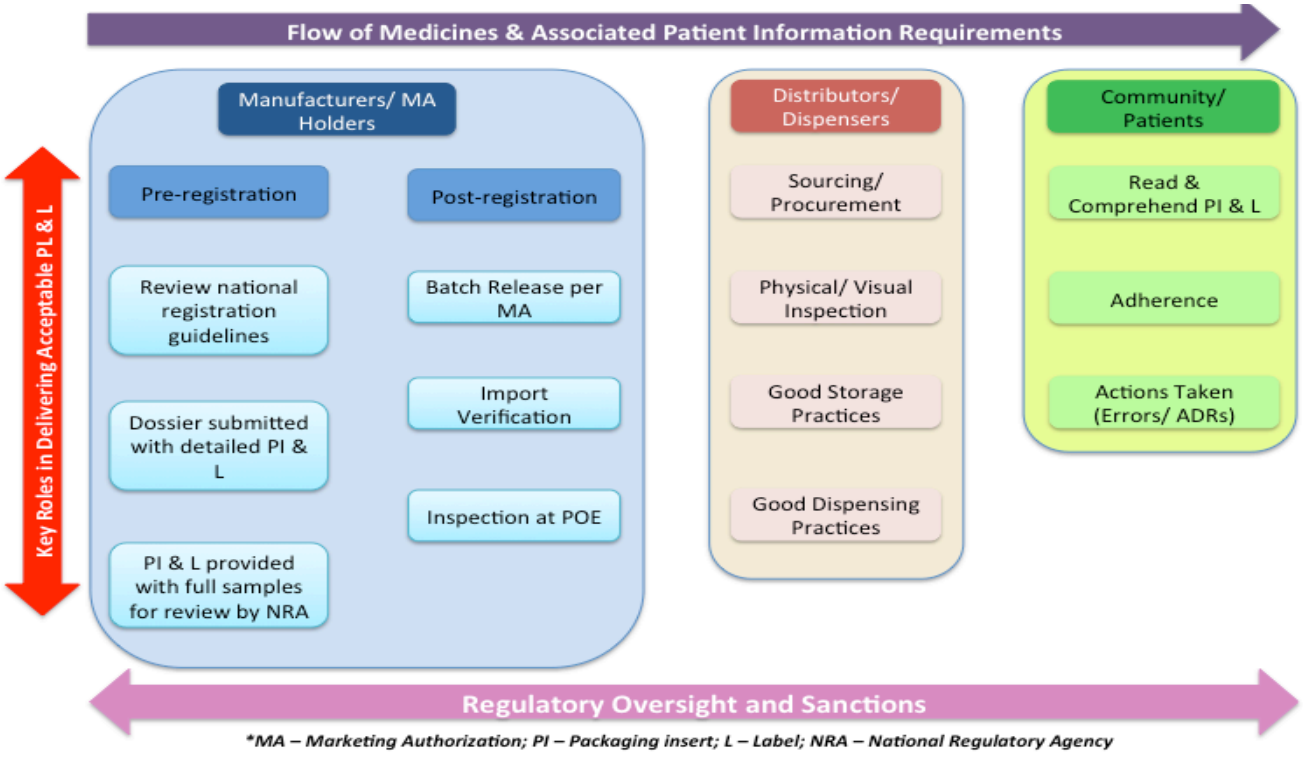

Figure 1: Context and Concept of the Project

In humanitarian and fragile contexts such as South Sudan, where regulatory oversight and post-marketing surveillance mechanisms are weak, every effort must be made to avail user-friendly information, including appropriate labels and PILs. However, manufacturers and their agents may disregard or compromise the quality of packaging information leaflets and labels once products are registered and authorized for distribution.

This study aimed to measure:

a) availability of tracer medicines in private pharmacies;

b) proportion of tracer medicines that were compliant with regulatory standards for labels and PILs;

c) proportion of patients who read the PILs provided with new or refilled medications;

d) proportion of patients who understood the content of the label and PILs for medicines dispensed to them.

2. METHODS

The study explored the relationship between availability of regulatory complaint labels and P, and patient comprehension of medicine information and rational use of products. Consideration was also given to examine moderating factors such as patient's level of education and sufficiency of patient counseling by dispensers.

A cross-sectional survey was conducted, collecting both quantitative and qualitative data from samples

purposively drawn from willing pharmacies in Juba, the capital city of South Sudan. Data was collected in one week in April 2018

The following approach was used for sampling and data collection:

- **Selection of tracer medicines:** Products on the World Health Organization (WHO) list of priority medicines for children and women (World Health Organization, 2012), or the UN Commission for Life Saving Commodities Report (United Nations, 2012) were selected. All the 17 eligible tracer medicines were asked for on the day of the survey at the pharmacies where data was collected. Where any of the tracer medicines were missing, no replacement was done with other products. However, to keep the sample size reasonable, it was decided for availability below 50%, an alternative pharmacy with better stock levels of the tracer medicines would be considered.
- **Selection of pharmacies**: Pharmacies were purposively selected based on their willingness to cooperate and allow data collection from their premises. Attempts were made to select at least one pharmacy in each of the 3 major Payams for Juba City Council. Data was collected from 5 pharmacies. One of these pharmacies also had a wholesale section, and another had a clinic in addition to the retail pharmacy. Consent for the assessment was obtained from all the in-charges at the five premises.
- **Selection of labels and PILs**: Labels and PILs to be reviewed were selected at two points: a) from the tracer medicines sampled for assessment of regulatory compliance; b) from dispensed packs of patients leaving the pharmacy. About 20-30 labels and PILs for tracer medicines and/ or those dispensed to patients were targeted for review, per pharmacy outlet, where data was collected. The labels and PILs were evaluated for compliance of with the European Commission Directive 2001/83/EC (European Economic Community, 1992) since South Sudan had not yet developed country-specific guidelines.
- **Selection of patients for exit interviews**: All patients who received any medicine dispensed from the collaborating pharmacy at the time of data collection were offered the opportunity to participate, with informed consent taken. Patients were selected sequentially on the day of the survey for interviews. For illiterate patients collecting medicines from the pharmacies, an accompanying attendant, if available, was given the PILs and asked questions. About 10-15 patients were targeted to be interviewed in exit interviews, per pharmacy outlet.

The tools used were validated in prior studies, but pre-testing was done to assess how well the adapted versions would apply to the local context:

- Checklist by Pires et al., (2015) for assessing regulatory compliance of the labels and PILs with the EC Directive 2001/83/EC.
- Flesh Readability Ease (FRE) formula, with reading scores on FRE scale are 0-100, for assessing patient comprehension of labels and PILs. Scores between 90 and 100 were considered easily understandable by an average 5th grader; between 60 and 70 were considered easily understood by 8th and 9th graders; and scores between 0 and 30 were considered easily understood by college graduates. The scores between 60 and 70 were largely considered acceptable ((Spadaro et al., 1980; Adepu R., and Swamy M.K., 2012).
- The Baker Able Leaflet Design (BALD) Method (Baker S., 1997; Shareef et al., 2016) was used to assess the layout and design characteristics of the patient information leaflets. The scores were based on the length of the line, distance between the line, letter font size, graphics used, percent of white space, and paper quality. The document is considered to have a good layout and design if it scored 25 or more.

The study did not collect private identifiable information. However, IRB approval for the study was obtained from the Purdue Ethics Committee (IRB# 1602017223).

3. RESULTS AND DISCUSSION

All the pharmacies were licensed by the regulatory authority. However, none of the superintendent pharmacists were present at time of assessment. Two had pharmacy technicians, while three had nurses in charge at time of assessment. The main sources of medicines for the pharmacies were imports from Egypt, India, and neighboring East African countries. Copies of importation documents were maintained on file at the premises.

Not all pharmacies prioritized inventory of essential medicines the way it is understood at the global level. Overall availability of the tracer medicines per pharmacy visited was 66%. Over 38% (14/37) of the tracer products had availability of less than, or equal to, 60%. Out of the 37 tracer medicines assessed, seven (19%) that require experts to administer in clinic settings (e.g., IUDs, calcium gluconate

injection, magnesium sulphate injection, misoprostol, oxytocin, and Ringer's lactate) were out of stock in all the pharmacies visited. This is probably because clinics in South Sudan generally do not refer prescriptions to pharmacies.

Availability of contraceptives was 100% for male condoms and emergency contraceptive pills, while Microgynon had availability 80%, Depo-Provera 60%, Implanon 60%, Jadelle 40%, and Microlut 40%. However, none of the pharmacies visited had female condoms, Sayana Press, or IUDs. Other life-saving maternal health medicines, such as oxytocin, misoprostol, magnesium sulphate, and calcium gluconate, which are vital for emergency obstetrics care, were not on the shelves at all. Essential child health medicines such as oral rehydration salt and zinc sulphate (for acute watery diarrhea) and dispersible amoxicillin (for pneumonia) were 100% available, while dispersible antimalarials were only available in 60% of pharmacies.

The selected tracer medicines address the biggest public health needs essential for reducing maternal and child mortality (Bigdeli et al., 2015). Access to such essential medicines is particularly critical in a country like South Sudan, where the World Bank and UN (2015) estimated maternal and child mortality to be 789/100,000 and 62/1000 respectively, ranking among the highest in the world. Availability and hence access through both public and private sector channels should be promoted for universal health coverage.

Labels were examined for a total of 97 products that were available in the four pharmacies, which gave consent for further assessment. Overall compliance was 79%. However, only 68% of PILs from these 97 products were found to be compliant with regulatory requirements.

Details of individual availability, and label and PIL compliance for each tracer medicine are presented in Table 1 below.

Table 1: Availability of Tracer Medicines in Pharmacies

S/ No.	Product	Availability	Label Compliance	PIL Compliance
TM -01	Artemether + Lumefantrine 20/120mg, 24 tablets	80%	80%	61%
TM -02	Artemether + Lumefantrine 20/120mg, 18 tablets	80%	80%	61%
TM -03	Artemether + Lumefantrine 20/120mg, 12 tablets	20%	27%	40%
TM -04	Artemether + Lumefantrine 20/120mg, 6 tablets	60%	80%	59%
TM -05	Artesunate 60mg/vial Injection	100%	82%	82%
TM -06	Sulphadoxine+Pyrimethamine 500/25mg Tablet	80%	80%	62%
TM -07	Male Condoms	100%	64%	17%
TM -08	Female Condoms	0%	0%	0%
TM -09	Oral Contraception – COC e.g. Microgynon	80%	72%	20%
TM -10	Oral Contraception – POP e.g. MIcrolut35	40%	82%	41%
TM -11	Injectables – Depo-Provera	60%	79%	62%
TM -12	Injectables – Sayana Press	0%	0%	0%
TM -13	IUDs	0%	0%	0%
TM -14	Implants - Jadelle	40%	84%	42%
TM -15	Implants - Implanon	60%	85%	0%
TM -16	Emergency contraception 1.5mg (x1) or 0.75mg(x2)	100%	71%	68%
TM -17	Ampicillin injection	100%	81%	83%
TM -18	Amoxicillin dispersible tablets, 250mg	100%	82%	83%
TM -19	Azithromycin tablets	100%	84%	83%
TM -20	Benzathine benzylpenicillin injection	100%	83%	80%
TM -21	Dexamethasone inj	80%	81%	61%
TM -22	Betamethasone inj	80%	81%	60%
TM -23	Calcium gluconate injection	0%	0%	0%
TM -24	Cefixime 400mg tablet	100%	82%	87%
TM -25	Chlorhexidine solution	80%	79%	42%
TM -26	Gentamicin injection	100%	80%	65%
TM -27	Hydralazine injection	100%	83%	63%
TM -28	Magnesium sulfate injection	0%	0%	0%
TM -29	Methyldopa tablet	100%	78%	64%
TM -30	Metronidazole injection	100%	84%	86%
TM -31	Misoprostol tablet	0%	0%	0%
TM -32	Nifedipine tablet/ capsule	100%	61%	85%
TM -33	Oral Rehydration Salt (ORS)	100%	79%	59%

S/ No.	Product	Availability	Label Compliance	PIL Compliance
TM -34	Oxytocin injection	0%	0%	0%
TM -35	Sodium lactate compound solution	0%	0%	0%
TM -36	Sodium chloride IV solution	100%	80%	48%
TM -37	Zinc sulfate tablet	100%	77%	75%
	Average score per pharmacy visited (%)	**66%**	**79%**	**68%**

Most of the products were manufactured in in India (59%), followed by China (31%). Few of them were from European countries such as Belgium (3%), Netherlands (3%), or Hungary (1%). A small proportion of products came from African countries: Kenya (1%) and Egypt (1%). Overall regulatory compliance of product labels was 79%. Hence using this as the minimum benchmark for a product to be considered compliant with labeling requirements by country of origin, it was noted only products from India (60%) were not compliant. In the same vein, considering the overall average for compliance with PIL requirements (68%) as the benchmark required for a product to be considered compliant with PIL requirements by country of origin, all products from other countries were 100% compliant, except India (57%).

Details of products by country of origin, and compliance with label and PIL requirements are presented in Table 2 below:

Table 2: Variation in product availability and compliance with labeling and PIL requirements by country of origin

Country	Products in Stock		Labeling Compliance		PIL Compliance	
	#	%	#	%	#	%
India	57	59	34	60	32	56
China	30	31	29	97	22	73
Belgium	3	3	3	100	3	100
Egypt	2	2	2	100	2	100
Netherlands	3	3	3	100	3	100
Kenya	1	1	1	100	1	100
Hungary	1	1	1	100	1	100
Total	**97**	**100**	**73**	**75**	**64**	**66**

With India and China, the main source of medicines in the private sector, it is important the DFCA applies risk-based screening and inspections on imports from these countries to curb poorly labeled products from entering the domestic supply chain.

In total, prescriptions from 13 patients, who left 4 pharmacies, were reviewed. The average products per prescription was 2.3, which is within acceptable limits for rational use of medicines, which is 2 to 3 medicines per patient per encounter according to WHO World Medicine Situation (2011). All the medicines were labeled prior to dispensing, but only 38% patients received PILs for all of their medications. This means once at home, patients had nothing to refer in case they forgot instructions given, or if they experienced side effects.

Details are summarized in Table 3 below.

Table 3: Review of Quality of Prescriptions

Pharmacy	Patient #	# Prescribed	All labeled?	All with leaflet?
1	P-01	5	1	0
	P-02	2	1	0
	P-03	2	1	1
	P-04	2	1	1
2	P-01	3	1	0
	P-02	3	1	1
	P-03	2	1	0
	P-04	2	1	0
3	P-01	3	1	0
	P-02	2	1	1
	P-03	1	1	0
	P-04	1	1	1
4	P-01	2	1	0
Total		30	13	5
Average		**2.3**	**100%**	**38%**

Client exit interviews were conducted with 12 patients from four pharmacies (same ones that provided PILs and allowed examination of labels from their premises). The demographic

characteristics of the patients are summarized in Table 4 below.

Table 4: Demographic Characteristics of Patients Interviewed

Sex		Age		Mother tongue		Present occupation		Education		Self-assessed reading ability	
Male	8	0-19	2	Acholi	1	Businessman	3	Primary school	2	Fair	5
Female	4	20-29	4	Bari	3	Housewife	1	Secondary school (O-Level)	5	Good	6
		30-39	3	Dinka	3	Social worker	1	Secondary school (A-Level)	2	Nil	1
		³40	3	Jur	1	Soldier	2	University	2		
				Kakwa	1	Student	3	Other (never been to school)	1		
				Kuku	1	Teacher	2				
TOTAL	12		12		12		12		12		12

All patients who received PILs with their dispensed medicines retained them, but only one read parts of the PIL before leaving the dispensing window, while the rest claimed they would read from home. Majority of the patients (83%) claimed they had previously used the medicines dispensed. When probed further if they normally read the PILs that come with their medicines, only 2 (16%) responded “Always,” with the rest responding with “Rarely” (58%) and “Never” (26%). All the patients interviewed had however asked the pharmacy staff about their medicine. Nevertheless, almost all (11 out of 12 [92%]) did not know if there were any occasions when the medicine should not be used. Additionally, 10 out of 12 (83%) were not sure what they should do if they forgot to take their medicine on time.

Review of patient understanding of PILs was done with four patients, who were willing to spend more time to read and answer questions on the PILs at the premises.

Table 5: Patient Understanding of PILs

Leaflet aspects assessed	Patient Responses
1. The letters in the text are:	Too small (1) – 25%
	Right size (3) – 75%
	Too small (1) – 25%
2. The distances between the lines are:	Right size (3) – 75%
3. The sentences in the text are (length):	100% right
4. The sentences in the text are (comprehension):	Easy (2) – 50%
	Difficult – 50%
5. Are there any words in the text that you do not understand	Few (1) – 25%
	Many (3) – 75%
6. Does the leaflet lack illustrations?	Don't know (3) – 7 5%
	No (1) – 25%
7. What does the leaflet say about the following?	
a) What is the medicine used for?	100% understood
b) How should you take it?	100% understood
c) In what way does the medicine act (work)?	50% understood

d) What is the name of the company that produces the medicine?	67% understood
8. Is there any other medicine that should not be taken together with your medicine?	25% understood, and knew the medicines that should not be taken together
9. Can your medicine be taken if the patient:	
Is pregnant?	50% Don't know
Is breastfeeding?	50% Don't know
Is going to drive a car?	50% Don't know
Has drunk alcohol?	50% Don't know
10. What do you do if you have taken too much medicine?	All did not know
11. Which side effects can your medicine give/ cause?	50% knew few side effects associated with their medicines
12. Are there any recommendations on how you should store your medicine?	75% knew storage conditions for their medicines
13. Is there anything that you would like to know about your medicine, which you cannot find in the leaflet?	No (4) – 100%
14. To find what I was looking for in the text was	Very difficult (1) – 25%
	Difficult (1) – 25%
	Easy (2) – 50%
15. I think that the leaflet as a whole is:	Easy (3) – 75%
	Difficult (1) – 25%
16. Any suggestions for improving the leaflet to make it easier for you to understand?	No idea (1) – 25%
	Fine (2) – 50%
	Make bigger (1) – 25%

These findings underscore the need for medicine regulation to go beyond legislating. It is important to create a regulatory enforcement and sanctions culture that will ensure manufacturers comply with conditions for marketing authorization. This will become more crucial with the growth of internet pharmacy and quality risks associated with it. For instance, in a similar study, Veronin (2011) obtained and evaluated a total of 41 drug products sourced from online pharmacies from 12 different countries and concluded only one product (from Canada) would meet both labeling and PIL guidelines for products allowed to be dispensed in the United States. This suggests labeling and packaging practices for some medicines sold online may be inferior to the high standards in the United States.

Another area to strengthen as part of good dispensing practices is the checking for patient understanding. At the moment, reading of PILs is very poor (only 16% *always* read them). This study showed patients may not understand instructions given at time of dispensing, but may fear to ask questions. Dispensers need to ask patients to relay back the information the way they understand it. They also need to orient patients on how and where they can find specific information on their patient information leaflets. This is particularly important in relation to side effects, contra-indications, interactions, dosage, and actions to take when doses are forgotten.

Finally, for PILs to be effective for patient education, they should be in simple language. Idris et al. (2014) who conducted a study among Sudanese community and hospital pharmacists cited texts' language (68.2%), technical terminology (75%), and font size (10%) as main barriers to understandability. Therefore, to secure usefulness of PILs, PILs should be written in lay terminology.

4. CONCLUSION

This exploratory study provides preliminary insight into the issues impacting access to life-saving medicines that are key to reducing maternal and child mortality in South Sudan. It also demonstrated gaps in the regulatory system, where the absence of a formal drug registration process leaves room for uncontrolled imports and potential dumping of counterfeit/sub-standard products in the country.

At the point of use, the study revealed several areas for improvement to ensure patients are empowered to use their medicines correctly for optimal therapeutic benefits. Dispensed medicines should be well labeled and accompanied by patient information leaflets that are easy to read and understand. Pharmacy staff should take time to educate patients on their medicines and encourage them to read the PILs.

5. RECOMMENDATIONS FOR NEXT STEPS

This study highlights existing regulatory and practice gaps in use of patient information leaflets and labeling for essential medicines distributed in Africa, and South Sudan in particular. The findings can support advocacy and campaigns that aim to:

a) encourage manufacturers to improve the quality of their labels and patient information;

b) improve patient understanding of their medicines, hence promote rational medication use;

c) reduce medication errors and improve therapeutic outcomes;

d) enhance overall patient safety.

The South Sudan Drug and Food Authority (DFCA) should put in place some mechanism for control of quality of products imported into the country even before a system of drug registration can be established. Developing a system for product notification can be a good starting point to ensure only notified products are allowed to be imported and distributed in the country. This can be followed for post-marketing surveillance that regularly assesses compliance of products in the market with minimum labeling and PIL requirements, and sanctions non-compliance.

Future studies with bigger and random sampling will be necessary to quantify and generalize the extent of the problem with poor quality of labels and PILs. Such studies should improve the data collection tools to capture more detailed differences in regulatory compliance and patient knowledge and practices in making use of product labels and PILs.

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ACKNOWLEDGEMENTS

I would like to thank all of the BIRS guest faculty from global industry and regulatory organizations for generously sharing their professional expertise and providing donated, in-kind time towards building the professional skills and technical capabilities of the students within the BIRS program. I would also like to thank my fellow peers in the BIRS MS student cohort for providing guidance and constructive feedback during the classroom group work and interactive sessions; Abigail Ekeigwe and Mercy Okezue, Purdue ABE BIRS PhD candidates, for their mentorship and input throughout the project; Professor Fran Eckenrode for providing content expertise throughout the review process on this paper; and Lauren Terruso, operations manager for BIRS Center, for all of her efforts on editing multiple iterations of the technical paper draft in preparation for publication. The international component of the Purdue BIRS program was initiated through educational support provided by the Merck Foundation and most recently through a capacity building effort funded by the Bill and Melinda Gates foundation, grant # 41000460.