African Journal of Pharmaceutical Research & Development

Vol. 12 No.1; pp. 070-078(2020)

EVALUATION OF CONTENT VALIDITY OF MEDICINE INFORMATION LEAFLETS IN PACKAGES OF ARTEMISININ-BASED COMBINATION THERAPY ANTIMALARIALS USED IN NIGERIA

RACHEL OBONOSE TITUS*, MARGARET OLUBUNMI AFOLABI AND OMONIYI JOSEPH OLA-OLORUN

Department of Clinical Pharmacy and Pharmacy Administration, Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife, Osun State, Nigeria.

ABSTRACT

Artemisinin-based-combination therapies (ACTs) are often used over-the-counter for treatment of malaria which is endemic in Nigeria. Study reports have shown that information contained in their medicine information leaflets (MILs), essential to achieving therapeutic outcomes, is oftentimes incomplete. The study evaluated the content validity of MILs of ACTs used in Nigeria and assessed the ordering of the pieces of information contained in them based on guidelines in the Summary Product Characteristics (SPC) of the Nigeria's medicine regulatory agency, National Agency for Food and Drugs Administration and Control (NAFDAC). The research was a descriptive cross-sectional study of 32 MILs of ACTs conveniently sampled over four months in pharmacies across four geopolitical zones of Nigeria. The NAFDAC-recommended SPC guidelines were enumerated to yield a 31-item evaluation guide which was employed for the evaluation. There were twenty-three (71.88%) of the thirty-one recommended information items in the thirty-two MILs with a mean content score of 24.17±2.57 which was significantly less (t = -15.99, df = 30, p=.000) than the expected test value of thirty-one. The difference between the mean content scores of the MILs of locally produced ACTs (23.22±2.32) and imported ones (25.11±2.80) was not statistically significant. The information contents were not always ordered as listed in the NAFDAC's SPC. The content validity of the information in the MILs of ACT antimalarials in Nigeria is suboptimal. Also, ordering of the information was irregular. Therefore, NAFDAC should be firmer in enforcing full compliance with their specifications for information contained in MILs.

KEYWORDS: **Medicine information leaflets, Content validity, Artemisinin-based combination therapies, Antimalarial, Self-medication, Self-care.**

INTRODUCTION

Artemisinin-based Combination Therapies (ACTs) are recommended by WHO for the treatment of malaria and are readily available to consumers in pharmacies for self-care. In the present information age with consumer rights and empowerment, access to high quality information about medicines satisfies consumers' rights to health information, particularly for those involved in self-care [1-3]. Consumer empowerment has been described as enhancement of consumers' ability to actively understand and influence their health status and the provision and access to adequate information [3,4]. In order to make informed decisions about their medication therapies, handy information resources such as medicine information leaflets (MILs) in medicine packages aid independent reference for consumers by helping them clarify possible doubts about the medicine use and thereby promotes safe and appropriate use of medicines [5,6]. Adequacy and accessibility of the information provided are key factors in satisfying this information need [1,7] and are considered to constitute a fundamental ethical, legal and professional obligation to consumers of medicines [2, 8].

Medicine information leaflets are recognised as complementary to healthcare professionals' verbal information [9], and serve as a valuable tool to educate patients about medicines. Provision of MILs

**Corresponding author:* obonose@gmail.com; +2348033823194

is recognised as an intervention strategy to improve medicine use among consumers [6,10]. Christudas *et al* [11] held that people retained about 20% of what they hear but that this could increase up to 50% if there is an added visual or written input. Written medicine information is thus an important source of information for consumers and a critical component of consumers' self-care [11,12]. For pharmacists, medicine information leaflets serve as a tool to enhance coverage of important details during patient counselling [13]. However, positive outcomes and treatment successes are undermined when MILs do not provide adequate information. This may result in reduced cure rates, relapse of disease, retreatment, development of adverse effects, hospitalization, development of resistance to the medication, loss of confidence in orthodox medicine and thus impede consumer satisfaction [2,9,14-16], defeating the goal of pharmaceutical care [17].

The World Health Organisation [18] prescribes that the content and quality of information provided for medicines and the mode of communicating the information remains a key element in educating consumers for responsible self-medication. Correct and sufficient information on medicines before use is one of the cornerstones of self-care [19]. Medicine information leaflets are required to be in conformity with the appropriate national medicine regulatory agency guidelines [19-22]. According to the recommendations of the Food and Drug Administration (FDA) in the US [23], the use of appropriate content and language is helpful to present information on risks more clearly. In the UK, current policy prioritises provision of comprehensive information for patients both as a right and a resource for effective self-care [24].

Malaria is endemic in Nigeria and consumers often self-medicate on ACTs purchased from medicine shops to treat episodes of malaria [25,26]. A majority or a sizeable proportion of medicines distributed in Nigeria are manufactured abroad [27]. Studies related to medication information documents have mostly shown omission of pertinent information as a problem [28-30]. However, very few of these studies based their evaluation on the medicine information guidelines of national medicines regulatory authorities. The objectives of this study were to evaluate the information content of the MILs and the information ordering based on the recommendations of the Nigerian National Agency for Food and Drug Administration and Control's (NAFDAC) Summary Products Characteristics (SPC).

MATERIALS AND METHOD

The study was a cross-sectional descriptive evaluation of medicine information leaflets of ACT antimalarials used in Nigeria. During the course of four months assigned for collection of the medicine information leaflets of ACTs, thirty-two MILs were conveniently sampled. Some ACTs where purchased directly from pharmacies in Oshogbo, Ibadan, Lagos and Ile-Ife and their MILs recovered for the study. Other MILs were obtained by post from pharmacists based on solicitation on a pharmacists' only WhatsApp group platform. They assisted in collecting and sending the leaflets from their shops across the country (Benin-City, Enugu, Ilorin, Jos and Okene).

The headings and sub-headings of the MIL information requirement section in the SPC of NAFDAC were enumerated to create a thirty-one key information items tabular checklist. The presence or absence of a piece of information was scored as 1 or 0, respectively. The scores were summed up for each leaflet to obtain the information content score. Counts were made on data about information content and correctness of statement about pertinent information such as dosing intervals. Assessment of the placement of information in priority order as outlined in NAFDAC's SPC were evaluated for MIL of each sampled ACT antimalarial. Each product was given a code label number to prevent identification.

Analysis and evaluation of the collected data employed both quantitative and qualitative methods. Descriptive statistics including frequencies, percentages and means, were employed to organise, summarise and present the collected data while questions about relations between variables were answered with inferential statistics at 5% level of significance. Thematic analysis was used for analysis of qualitative data collected.

Ethical Approval

Ethical approval was not obtained as the study did not employ human subjects as respondents and the information is publicly available.

RESULT

The results are presented in Tables 1- 3. Out of the thirty-two MILs sampled, 11(34.4%) were "for adult only" preparations, 8(25%) were "for children only" preparations and 13(40%) were for both adult and children preparations (Table 1). The modal combination types were the artemether20mg +

Lumefantrine 120mg (50%) and the artemether 80mg+ Lumefantrine 480mg (21.9%) strengths. The least common combinations were the artesunate 200mg+Sulphamethoxypyrazine 500mg, arteroline 150mg+amodiaquine 750mg and the dihydroartemisinin 40mg + piperaquine phosphate 750mg which were 3.1% each among the sampled products. The imported ACT antimalarials (84.38%) were more than the locally manufactured brands of which a dominating proportion (59.38%) were imported from India. Three of the products were manufactured in China (9.4%), one product (3.1%) each from Italy and Morocco while five products (15%) were manufactured locally.

Eleven (35.48%) out of the thirty-one information items were present in all the thirty-two MILs (Table II) yielding an average content score of 23.75±0.45 (≈24) for the MILs which is significantly ($t = -15.99$, $df = 31$, $p = .000$) lower than the total number of the pieces of information enumerated in the NAFDAC-SPC. The least (28.13%) frequently stated information was contact "phone number". Less than half (46.9%) of the MILs reported the last date of revision of the text while 68.75% had entries for excipients.

ACT products content validity scores

None of the MILs scored 100% in content validity. ACT7 had the highest percentage content validity (93.55%) followed by ACT8 (90.32%). The three products, ACT9, ACT10 and ACT21 each scored 87.01%. The average content validity score for all the MILs was 24.16 which was significantly ($p=0.000$) lower than the expected test value of 31.

The MILs of two products ACT24 and ACT29 had the least content validity score of 61.29%. Independent t-test analysis result showed no significant difference ($t= 1.96$; $df = 30$, $p= 0.06$) between the average content validity score of the MILs of imported ($x = 23.22±2.32$) ACT antimalarials and those manufactured locally ($x =25.11±2.80$).

Information ordering in the medicine information leaflet

The sampled MILs contained different information on the dosing intervals of the medicines. Among the Artesunate + Lumefantrine combinations, only a few (18.8%) had the dosing intervals in their MILs stated correctly indicating the 8-hour interval between the first and second dose, 24-hour interval between the first and third dose and subsequently a 12-hourly interval. Some stated the dosing interval as a morning and evening dosing regimen only while others indicated the 8-hour interval between the first and second dose but failed to instruct that the third dose is to be taken 24-hours after commencement of the treatment (first dose). The "Once daily" dose instruction in MILs of the Artesunate+Amodiaquine generics did not specify the 24-hours needed between doses. Majority (56.3%) of the MILs of the ACT antimalarials did not order the information in the MILs as outlined in the SPC of NAFDAC which placed the information on indications at the initial section of the leaflet immediately after the section on Composition and Pharmaceutical formulation. The MILs of some (43.75%) of the ACTs like ACT11, ACT15 and ACT14 had the information placed at a later section of the MIL after headings such as pharmacodynamics and pharmacokinetics.

The MILs of two products, ACT8 and ACT7 have two sections each. The information in the first section addressed health professionals and complied with the NAFDAC SPC format while the second section titled, "Information for the User" was shorter and devoid of technical terms. It started with an instruction to read the leaflet before using the medicine and to keep the MIL for further reading. The instructions were written under six headings of which two were expressed as questions as follows (unedited):

1. *What ACT8 is and what is it used for?* Which corresponds to information on Description and Indication.
2. *Before you take ACT8.* This section was on contraindications, drug interactions, caution on use during pregnancy and lactation and effects of medicine on driving and the use of machines.
3. *How to take ACT8* This section corresponded to the SPC section on dosage and administration, what to do if there was an overdose and what to do if consumer forgot to take the medicine at the right time.
4. *Possible side effects.* This listed the side effects, adverse effects and the probability of experiencing such adverse effects.
5. *How to store ACT8?* This section was about storage, use beyond expiry date and disposal methods for unfinished medicines.

Table 1: Description of the ACT antimalarials products collected

S/N	Product Code Name	Type of dosage form	Active Ingredients	Country of Manufacture
1	ACT1	Tablets	Artemether20mg +Lumefantrine180mg	Nigeria
2	ACT2	Tablets	Artemether80mg +Lumefantrine480mg	India
3	ACT3	Tablets	Artesunate100mg+Amodiaquine270mg	China
4	ACT4	Tablets	Artesunate100mg+Amodiaquine300mg	China
5	ACT5	Tablets	Artesunate200mg+ Sulphamethoxypyrazine500mg+ Pyrimethamine25mg	Italy
6	ACT6	Tablets	Artemether20mg/Lumefantrine480mg	India
7	ACT7	Bilayered Uncoated Tablets	Artesunate100mg+Amodiaquine270mg	India
8	ACT8	Tablets	Artemether20mg+Lumefantrine120mg	India
9	ACT9	Tablets	Artemether 20mg+Lumefantrine120mg	India
10	ACT10	Tablets	Arterolane 150mg+ Piperaquine phosphate750mg	India
11	ACT11	Tablets	Artemether20mg+Lumefantrine120mg	India
12	ACT12	Tablets	Dihydroartemisin 40mg +Piperaquine320mg	India
13	ACT13	Tablets	Artemether 80mg +Lumefantrine480mg	India
14	ACT14	Tablets	Artemether80mg +Lumefantrine480mg	India
15	ACT15	Tablets	Artemether20mg +Lumefantrine120mg	India
16	ACT16	Tablets	Artemether40mg +Lumefantrine240mg	Nigeria
17	ACT17	Tablets	Artemether80mg+Lumefantrine480mg +Paracetamol 500mg	Nigeria
18	ACT18	Tablets	Artemether80mg+Lumefantrine480mg	India
19	ACT18	Tablets	Artemether20mg +Lumefantrine120mg	India
20	ACT20	Tablets	Artemether20 +Lumefantrine120mg	Country specific
21	ACT21	Tablets	Artemisinin62.5mg+Piperaquine375mg	China
22	ACT22	Caplets	Artemether80mg +Lumefantrine480mg	India
23	ACT23	Tablets	Artesunate50mg+Amodiaquine135mg	Morocco
24	ACT24	Tablets	Artemether 80mg+Lumefantrine480mg	Nigeria
25	ACT25	Tablets	Artemether 20mg+Lumefantrine120mg	India
26	ACT26	Dispersible Tablets	Artemether 20mg+Lumefantrine120mg	Country Specific
27	ACT127	Powder for Oral Suspension	Artemether 20mg+Lumefantrine120mg	India
28	ACT28	Powder for Oral Suspension	Artemether 20mg+Lumefantrine120mg	India
29	ACT29	Tablets	Artemether20mg +Lumefantrine120mg	Nigeria
30	ACT30	Tablets	Artemether20mg +Lumefantrine120mg	India
31	ACT31	Tablets (Children only)	Artemether20mg+Lumefantrine120mg	India
32	ACT32	Dispersible tablets	Artemether 20mg+ Lumefantrine 120mg	India

Table 2: Proportion of Pieces of Information in the MILS of ACT antimalarials based on NAFDAC-SPC

S/N	Information items	Frequency		%
		No	Yes	
1	Name of the product	0	32	100
2	Strength of the product	0	32	100
3	Pharmaceutical form	0	32	100
4	Name of the active substance	0	32	100
5	Therapeutic indication	0	32	100
6	Posology	0	32	100
7	Method of administration	0	32	100
8	Contraindications	1	31	96.88
9	Precautions for use	0	32	100
10	Interaction with other medicinal products	0	32	100
11	Use in pregnancy	1	31	96.88
12	Use during lactation	2	30	93.75
13	Effect on ability to drive machines	17	15	46.88
14	Undesirable side effects	3	29	90.63
15	What to do in the event of an overdose	3	29	90.63
16	Statements on side effects, including allergic reactions	2	30	93.75
17	Pharmacodynamic properties stated	3	29	90.63
18	Pharmacokinetic properties stated	4	28	87.50
19	Preclinical safety data stated	16	16	50.00
20	List of excipients	10	22	68.75
21	Any major incompatibility	0	32	100
22	Shelf life	17	15	46.88
23	are special precautions on storage	0	32	100
24	Is the nature and the content of the container	4	28	87.50
25	Special precaution on disposal of used product	11	21	65.63
26	Is the marketing authorization holder	1	31	96.88
27	Marketing authorization number (NAFDAC number)	8	24	75.00
28	Date of the first authorization or renewal of the authorization	20	12	37.50
29	Last date of revision of text	17	15	46.88
30	Translation into any of the local languages	32	0	0.00
31	A contact phone line or Email address	23	9	28.13

Table 3: Percentage and frequency of the information items contained in the MILs based on NAFDAC-SPC guideline

S/N	Product Code Name	*Total Score of content for each MIL	% Content Validity Score
1.	ACT7	29	93.55
2.	ACT8	28	90.32
3.	ACT9	27	87.01
4	ACT10	27	87.01
5	ACT21	27	87.01
6	ACT6	26	83.87
7	ACT13	26	83.87
8	ACT15	26	83.87
9	ACT11	25	80.65
10	ACT12	25	80.65
11	ACT23	25	80.65
12	ACT32	25	80.65
13	ACT25	25	80.65
14	ACT14	24	77.42
15	ACT20	24	77.42
16	ACT22	24	77.42
17	ACT26	24	77.42
18	ACT28	24	77.42
19	ACT30	24	77.42
20	ACT4	23	74.19
21	ACT5	23	74.19
22	ACT18	23	74.19
23	ACT17	22	70.97
24	ACT19	22	70.97
25	ACT2	21	67.74
26	ACT3	21	67.74
27	ACT16	21	67.74
28	ACT27	21	67.74
29	ACT31	21	67.74
30	ACT1	20	64.52
31	ACT24	19	61.29
32	ACT29	19	61.29

6 *Further information.* Here the composition of the medicine and the excipients were listed.

For ACT7 and ACT8 MILs, the length of the second section is less than a third of the first and devoid of technical jargons.

DISCUSSION

General features of the MILs

The compositions of the active ingredients in the ACTs sampled in this study is a reflection of the combinations available for use. The high number of the Artesunate 20mg + Lumefantrine 120mg combination showed the predominance of this combination in the treatment of uncomplicated malaria which studies have been shown to be the most tolerated of the ACTs [30]. The availability of 'paediatrics only'' ACT medicines assures that age-appropriate dosages can be given to children who need it [31]. This prevents under-dosing with attendant consequence of treatment failure and avoids overdosing with risk of precipitation of adverse reactions.

Adequacy of Information in the MILs

Compliance of all the MILs with only 23 of the 31 items of the NAFDAC SPC shows that the information content of the MILs needs to be improved upon. The implication of this is that pertinent information which are not adequately supplied could have dire consequences for consumers who need to make correct decisions based on the information. For example, the instruction that the medicine should be taken once daily is not sufficient for the consumer who may take a dose in the night and another in the morning not observing a 24-hours interval resulting in high doses in the systemic circulation and attendant adverse reactions.

The fact that the locally produced ACTs had a lower average number than the imported products may reflect the lower number of locally manufactured products in the market. It also showed that both locally and foreign produced ACTs need to be improved to be more compliant with regulations and to agree with the WHO [31] position on the issue which states that the combined efforts of industry and regulators must meet the expectations of consumers by providing products which are safe, effective, good value for money, and accompanied by complete and relevant information. High ethical standards should be applied to the provision of information, promotional practices and advertising. The content and quality of such information and its mode of communication remains a key element in educating consumers in responsible self-medication. The non-listing of the excipients in some MILs is an omission of important consequence for consumers who could be allergic to some of the constituents of the excipients in the medication. This could be detrimental to the health of individuals sensitive to any of the excipients in the formulation. Young children whose caregivers often patronise drug sellers [32] are particularly at risk. It has been reported by some studies [33,34] that some excipients exert pharmacological effect and asthmatics and young children could be adversely affected by their use of medications containing such excipients. Hence, there is need to list them so that susceptible persons can be informed of the constituents and avoid consuming the ACT antimalarial.

Qualitative analysis of the MILs showed that information about dosing intervals was not clear. Once daily is not a clear instruction, as consumers could take the recommended dose in the night and for convenience or ignorance take another dose of the medication the next morning assuming that the once daily dosing has been satisfied for the two days. This information is an important feature that helps consumers space out medicine correctly to avoid medicating haphazardly with its consequent toxicity.

The placement of information such as "indication" in a later section as different from the ordering of information items in the SPC does not make it immediately accessible and visible to the reader. This may not be a good way to present information as accessibility to information motivates the reader to read on and make prompt use of it. Though a few of the MILs (ACT18, ACT21 and ACT 17) also placed this information in a later section, the preceding sections were very short (ACT17, 12 lines), the headings were of sharp contrast to the body of the text (ACT21) and the leaflet was of a very short length (ACT18,12cm by 6cm). These made the information easily noticeable to the reader. However, it can be said that placing the information in an earlier section makes for smoothness in reading and a better flow of items. It also shows the importance of knowing what the medicine is used for before going into its pharmacodynamics or other information about the medicine.

The provision of two sections in the MILs of two of the products is an appreciation that readers may be of diverse background. Consumers who are not health professionals or who do not understand the

jargons in the technical section would find the simplified version of the MIL in the second section for their medicine information useful.

The limitations of the study

A gap observed during analysis and discussion of the study was that the phone lines and Email addresses provided by some (23.17%) of the MILs were not verified as operational or not. A further study could objectivize this limitation to ascertain this.

CONCLUSION

The study has shown that the content validity of the medicine information leaflets of the ACT antimalarial medicines used in Nigeria was suboptimal as the MILs did not fully comply with the SPC of NAFDAC. Thus, there is need for regulatory authorities to be firmer in enforcing full compliance with their specifications.

ACKNOWLEDGEMENT

The authors acknowledge the kind support of all colleagues who sent MILs via courier from different parts of the country. No funding was received for this study.

REFERENCES

1. Mottram DR, Reed C. Comparative evaluation of patient information leaflets by pharmacists, doctors and the general public. *Journal of Clinical Pharmacy and Therapeutics*, 22(2),1997:127–34.
2. Ngoh LN. Health literacy: a barrier to pharmacist-patient communication and medication adherence. *Journal of American Pharmacists Association*, 49(5), 2009: e132-e146.
3. McAllister M, Dunn, G, Payne, K., Davies, L, Todd, C. Patient empowerment: the need to consider it as a measurable patient-reported outcome for chronic conditions. *BMC Health Services Research*, 12, 2012:157.
4. Rodwell CM. An analysis of the concept of empowerment. *Journal of Advanced Nursing*, 23,1996:305-313.
5. Afolabi MO, Afolabi ER, Ojedokun OE, Adediwura AA. Content Validity and Readability Estimates of Selected Leaflets Sold Over the Counter in Nigeria. *The African Symposium*, 10 (1), 2010:34- 41.
6. Management Sciences for Health. MDS-3: Managing Access to Medicines and Health Technologies. Arlington, VA: Management Sciences for Health. Chapter 27, Managing for Rational Drug Use, 2012: 524.
7. Zwaenepoel L, Bilo R, De Boever W, De Vos M, Reyntens J, Hoorens V, Sermeus W, Laekeman G. Desire for information about drugs: a survey of the need for information in psychiatric in-patients. *Pharmaceutical World Science,* 27, 2005:47-53.
8. Raynor DK., Blenkinsop A, Knapp P, Grime J, Nicolson DJ and Pollock K. A systematic review of quantitative and qualitative research on the role and effectiveness of written information available to patients about individual medicines. *Health Technology Assessment,* 11(5), 2007:1–160.
9. Poornima D and Ramesh A. (2014). Assessment of Patient Information Leaflets Usefulness in Selected Chronic Diseases – A South Indian Based Study. *Indian Journal of Pharmacy Practice,* 7(1), 2014:23.
10. Hughes CM, McElnay JC and Fleming GF. Benefits and risks of self-medication. *Drug Safety*, 24, 2001: 1027–1037.
11. Christudas M J, Isaac NM, Ramesh A, Varghese NA, Abraham LS, Kurian J and Narahari MG. Assessment of patient information leaflets (PIL) usefulness in patients with chronic diseases- A randomized controlled study. *World Journal of Pharmacy and Pharmaceutical Sciences,* 5 (2), 2016: 931-940.
12. Duman M. Producing patient information: how to research, develop and produce effective information resources. King's Fund, London, 2003: 140.
13. World Health Organisation. Declaration on the Rights of the Patient, World Malaria Report. WHO Press, World Health Organization, 1, 2011:137.
14. Holmalahti J. What Does Drug Packaging Tell Us About its Contents? *Pharmaceutical Technology.* Europe, 2004.
15. Kasesnik K and Kline M. Analyzing readability of medicines information material in Slovenia. *Southern Medical Review*, 4(2), 2011: 80–87.
16. Gyasi WK. Readability and Health Communication: An Analysis of the Readability of Commonly Used Malaria Drugs Information Leaflets in Cape Coast, Ghana. *IOSR Journal of Research and Method in Education,* 2 (4), 2013:17-25.
17. Helper DD and Strand LM. Opportunities and Responsibilities in Pharmaceutical Care.

American Journal of Pharmaceutical Education, 1989: 53.
18. World Health Organization. Guidelines for the regulatory assessment of Medicinal Products for use in self-medication. WHO/EDM/QSM/00.1, 2000.
19. Ozolina V. Study of accessibility and quality of the patient information about medicines in Latvia. SHS Web of Conferences 2, 00024, EDP Sciences 2012. http://dx.doi 10.1051/shsconf/20120200024.
20. European Parliament and Council of the European Union. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. *Journal of European Communication,* 2001: 67-128.
21. Medicines and Healthcare products Regulatory Agency (MRHA), Committee on Safety of Medicines. "Always Read the Leaflet Getting the best information with every medicine. Report of the Committee on Safety of Medicines Working Group on Patient Information". Annex 6, The Stationery office, London, 2005: 97-111.
22. Raynor DK, Dickinson D. Key principles to guide development of consumer medicine information – content analysis of information design texts. *Annals of Pharmacotherapy*, 43, 2009: 700-706. http://dx.doi.org/10.1345/aph.1L522.
23. NAFDAC. Common Technical Document Requirements (adapted from The West African Health Organization (WAHO-Ctd.) September 2013. Retrieved at http://www.nafdac.gov.ng/images/Guidance_Document_on_the_COMMON_TECHNICAL_DOCUMENTS_for___Industry.pdf
24. Europeans Medicines Agency. Quality Review of Documents Group: QRD Annotated Template: Revision of the Product information. London. 2010.
25. Afolabi AO. Factors influencing the pattern of self-medication in an adult Nigerian population. *Annals of African Medicine*, 7(3), 2008:120-127.
26. Osemene KP and Lamikanra, A. A Study of the Prevalence of Self-Medication Practice among University Students in Southwestern Nigeria. *Tropical Journal of Pharmaceutical Research*, 11 (4), 2012: 683-689. http://dx.doi.org/10.4314/tjpr.v11i4.21
27. Ugbam OC and Okoro EA. A Strategic Study of the Nigerian Pharmaceutical Sector: Organizational Leadership, Market-share, and Competitive Performance. *International Journal of Business, Humanities and Technology,* 7(1), 2017.
28. Raynor DK, Svarstad B, Knapp P, Aslani P, Rogers MB, Koo M, Krass I, Silcock J. Consumer medication information in the United States, Europe, and Australia: a comparative evaluation. *Journal of American Pharmaceutical Association,* 47(6), 2007:717-24.
29. Maat HP and Lentz L. Improving the usability of patient information leaflets. *Patient Education Counselling,* 80(1), 2010:113-9. Doi:10.1016/j.pec.2009.09.0301
30. Etchells E. A safe, effective adjunctive treatment for arthritis, and pretty much every other condition you'll ever treat. *Journal of Rheumatology,* 26, 1999:1647–9.
31. World Health Organization: Report of the WHO Expert Committee on National Drug Policies. 1995 http://www.who.int/medicines/library/dap/who-dap-95-9/who-dap-95.9.shtml
32. Gyapong M, Garshong B, World Health Organization and UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. Lessons learned in home management of malaria: implementation research in four African countries, 2007. https://apps.who.int/iris/handle/10665/43617
33. Golightly, Pharmaceutical Excipients Adverse Effects Associated with Inactive Ingredients in Drug Products (Part I). *Medical Toxicology,* 3, 1998:128-165.
34. Cordner C, Caldwell N and Elliot P. What else is in our children's medicine? *Archives of Disease in Childhood,* 97, 2012:2-3.