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Research Article

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Regulatory Compliance of Small-Scale Pharmaceutical manufacturing facilities in Addis Ababa, Ethiopia

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Abstract

Background: there is growing concern that medicines supplied to most of the developing countries are of substandard quality. Along with the establishment of strong regulatory systems for ensuring compliance and regulatory law enforcement, manufacturing facilities need to work to implement dependable systems at each stage of the production process to ensure the safety, efficacy, and quality of their products. Objective: the aim of this study was to assess the level of compliance with regulatory requirements by small-scale pharmaceutical manufacturing facilities in Addis Ababa, Ethiopia.

Material & Method: A cross-sectional observational study was conducted using a structured questionnaire and checklist to assess the level of compliance of small-scale local pharmaceutical manufacturing facilities to regulatory requirements and also to identify the challenges faced by the manufacturing facilities.

Result: This study indicated that the overall implementation status of regulatory requirements in the local small-scale pharmaceutical manufacturing companies is far below the minimum standard set by WHO and the national regulatory authority. Basic on specific regulatory requirement elements compliance: requirements related to QA were 26.9, requirements related to personnel qualification were 38.1, requirements related to Quality control were 25.9, and requirements related to sanitation and hygiene were 15.3. Of the total regulatory requirements, only 26.1% were found to be implemented. Major challenges faced by the local small-scale pharmaceutical manufacturing industry for the implementation of regulatory requirements were: human resource capacity constraints, limited investment, limited support from Governments and other stakeholders, and poor infrastructure.

Conclusion: The study demonstrated that level of regulatory requirements implementation in the local small-scale pharmaceutical manufacturers is far below the minimum standard set by the national regulatory authority. Important gaps were reported particularly in materials management, production operations, quality control, and sanitation and hygiene.

Keywords: Good manufacturing practices, Quality medicines, Regulatory compliance, Regulatory requirements, Small-scale manufacturers

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1. Introduction

Despite accounting for about 85% of the world population, developing regions share only 21% of pharmaceuticals both in terms of production and consumption. (1, 2) The industry is globalizing its spectrum in order to improve stocks of raw materials to be used in global production and to improve skills and research capability; however, the contribution from low-income countries, particularly in sub-Saharan Africa is still staggering. (3, 4) The weak experience of developing countries in pharmaceutical production is associated with the lack of infrastructure, finance, and technical capacity to independently produce the drugs that they need. (5) Local manufacturing has been considered a potential solution to sustainably address access and availability problems for essential medicines. Similarly, small-scale local pharmaceutical manufacturing facilities have a significant contribution to global healthcare as they supply healthcare supplies and extemporaneous preparations; which otherwise may not be the focus areas for large-scale pharmaceutical companies. (6,7) Ethiopia is the second-most populous country in Africa with increasing demand for pharmaceutical products. However, the production of

pharmaceutical products in Ethiopia is quite small and covers not more than 15 to 20% of the national demand for essential medicines. Currently, there are 11 actively operating local industries engaged in the large-scale production of pharmaceuticals in Ethiopia. There are also several small-scale manufacturing facilities concentrated mainly concentrated in Addis Ababa and its outskirts engaged in the production of healthcare supplies such as disinfectants, antiseptics, and laboratory reagent solutions. The facilities often claim that they are facing challenges associated with physical infrastructure, financing, and technical capacities which are limiting their development and sustainability. On the other hand, relevant stakeholders including regulatory bodies and health professionals often raise concerns regarding the quality and manufacturing practices of such facilities. Recognizing their essential role in national healthcare, the government and other stakeholders have been providing support to build the capacity of the facilities and facilitate technology transfer in the sector. (8)

According to the Ethiopian Food and Drug Authority (EFDA), small-scale pharmaceutical manufacturers are facilities engaged in processing or production of products for external use only including sanitary items, cosmetics, disinfectants/antiseptics, medical supplies, and related products using none sophisticated technology. (9) The authority has a mandate and responsibility to ensure that all pharmaceutical value chain players involved in clinical research, laboratory testing, manufacturing, import/export, distribution, and retail should conform to acceptable local and international standards. (10) EFDA developed a directive for small-scale pharmaceutical manufacturing facilities to ensure products manufactured in small-scale establishments are up to the required safety, quality, and efficacy. In the directive, minimum requirements with respect to practices, premises, professionals, and products are defined to ensure adherence to Good Manufacturing Practices and Good Laboratory Practices. (11)

The manufacturing facilities are hence expected to be compliant with such minimum requirements to ensure that their products are safe and of acceptable quality. (12) Establishing and implementing detailed written procedures, documentation and archiving systems, and quality assurance mechanisms at the various stages of production are essential elements of the requirements.

The purpose of this study was to assess the level of compliance to regulatory requirements established by EFDA of small-scale pharmaceutical manufacturers found in Addis Ababa.

2. Methodology

Study design

A cross-sectional quantitative study was conducted to assess the level of compliance to established regulatory requirements and identify the major challenge faced by local small-scale pharmaceutical manufacturing facilities.

Study area and scope

There are 46 small-scale pharmaceutical manufacturing facilities licensed by EFDA. This study was conducted in 18 of the local small-scale pharmaceutical manufacturers based in Addis Ababa. Data were collected starting from September 2019 up to October 2019. The study is limited to purposively selected facilities that are categorized as small-scale pharmaceutical manufacturing facilities by the national regulatory authority and engaged in the production of healthcare supplies such as disinfectants/antiseptics, laboratory reagents, and cosmetics. The findings of the study reflect the regulatory and quality manufacturing practices and compliances level of small-scale pharmaceutical manufacturing facilities and cannot be extrapolated to large-scale manufacturing companies and others operating out of Addis Ababa.

Sample size and sampling procedure

The eighteen pharmaceutical manufacturing companies that manufacture extemporaneous pharmaceutical preparations, laboratory reagents, and disinfectants were included in the study. All active functional small-scale manufacturers during the study period were included. Technical experts working in the selected facilities who directly or indirectly involve in the implementation of quality systems and regulatory requirements within their respective companies were included in the study.

Data collection instruments

For the collection of required data, an observational checklist adopted from the EFDA minimum standard requirements established for small-scale manufacturing facilities (2014), and WHO Technical Report Series, No. 961(2011)) were used. Data were collected by trained data collectors who have B. Pharm professional background and adequate training and knowledge in the manufacturing area. In order to investigate challenges faced by the facilities in implementing quality and regulatory requirements, a structured self-administered questionnaire was used. The questionnaire was pre-tested on 5 technical experts working in small scale pharmaceutical manufacturing facilities which were not included in the final study. Appropriate modifications were made based on the feedback obtained from the pre-testing.

Data Entry and Analysis

All the data collected by the data collectors were closely supervised and daily checked by the principal investigators for accuracy and completeness. After data cleaning procedures, data were entered into a computer and analyzed using a Statistical Package for the Social Sciences software (SPSS, version 22). Results were presented in the form of tables, graphs, and descriptive narrations as appropriate. The level of quality implementation and regulatory compliance by the facilities for specific requirements are rated as full implementation for companies that show the implementation of all the requirements; partial implementation for companies

that have evidence of implementation of some requirements; and no implementation for companies that could not implement any of the requirements.

Operational definitions

- **Fully implemented**: Implementation of all specific regulatory requirements set by the Ethiopian Food and Drug Authority (EFDA) directive and WHO Guideline.
- **Partially implemented**: Among the established regulatory requirements set by the Ethiopian Food and Drug Authority (EFDA) directive and WHO Guideline, some elements are implemented by the manufacturers.
- **Not implemented**: None of the regulatory requirement elements set by the EFDA and WHO are implemented
- **Regulatory compliance**: Full implementation of the requirements of premises, equipment, personnel, documentation, sanitation, and hygiene.
- **Small-Scale pharmaceutical manufacturers**: manufacturers classified as small-scale by the EFDA and involved in processing or production of products for external use only, including sanitary items, cosmetics, antiseptics/disinfectants, medical supplies, and related products using none-sophisticated technology.

3. Results

Background characteristics of study facilities and participants

The present study investigated eighteen small-scale pharmaceutical manufacturing companies with an operational history of 1 to 24 years and all manufacturing human medicines, reagents, and disinfectants. With regard to their business arrangement, 17 (94.4%) are privately owned local firms while the remaining one is a private joint venture entity with foreign investors.

Table 1. Basic information of the company included in the study (N=18)

S. No.	Company code	Year of establishment	Product category	Business Arrangement
1.	01	2014	Disinfectant, reagent, Human medicine	Private by local people
2.	02	2012	Disinfectant, reagent,	Private by local people
3.	03	2009	Disinfectant, reagent,	private by local people
4.	04	2001	Disinfectant, reagent,	private by local people
5.	05	2005	Disinfectant,	private by local people
6.	06	2004	Reagent,	private by local people
7.	07	2007	Disinfectant, reagent, Human medicine	private by local people
8.	08	2016	Disinfectant, reagent, Human medicine	private by local people
9.	09	2016	Disinfectant, reagent,	private by local people
10.	10	2010	Disinfectant, reagent, Human medicine	private by local people
11.	11	2013	Disinfectant, reagent,	private by local people
12.	12	2015	Disinfectant, reagent,	private by local people
13.	13	2006	Disinfectant, reagent, Human medicine	Private joint venture with foreigner
14.	14	2015	Disinfectant, reagent,	Private by local people
15.	15	2014	Disinfectant, reagent, Human medicine	Private by local people
16.	16	2012	Reagent	Private by local people
17.	17	2011	Disinfectant, reagent, Human medicine	Private by local people
18.	18	2015	Disinfectant, reagent, Human medicine	Private by local people

Of the technical experts who participated in the study, more than half (61.1%) were male with a mean age of 41.63 ± 12.54 years. The detailed characteristic information of the study participants is presented in Table 1. The majority of them, 11(61.1%) have over 5 years of work experience in the current company.

Table 2. Basic characteristics of study (N=18)

Variables	Category	Frequency	Percentage
Sex	Male	11	61.1
	Female	7	38.9
Mean age (years)	41.63 ± 12.54		

Total work experience (years)	≤5	3	16.7
	6-15	11	61.1
	>15	4	22.2
Primary responsibility at the current	Production manager	8	44.4
	Quality control	4	22.2
	Chief executive officer	2	11.1
	Technical manager	2	11.1
	General Manager	2	11.1
Highest academic qualification	BSc degree	14	77.8
	MSc	3	16.7
	PhD	1	5.6

In the current study, regulatory compliance requirements were grouped into 8 composite categories encompassing two or more regulatory compliance elements. A relatively higher level of implementation (55.6%) was observed in requirements related to documentation of storage of reference/retention samples including the availability of responsible personnel and documented procedures for receiving, storing, and sufficient testing of raw materials. Availability of adequate and qualified personnel was mentioned in 50% of participants and the rest response was described in Table 2.

Table 3. Participant's responses on regulatory compliance elements (N= 18)

Regulatory compliance element	Specific regulatory requirements	FI N(%)	PI N(%)	NI N(%)
Materials management	Use of procedures/SOPs for receiving and storage of raw materials	9 (50.0)	0 (0)	9 (50.0)
	Availability of list of approved raw material suppliers	5 (27.8)	6 (33.3)	7 (38.9)
	Use and documentation of specifications for each raw material	3 (16.7)	10 (55.6)	5 (27.8)
	Conducting sufficient testing on raw materials	9 (50.0)	7 (38.9)	2 (11.1)
Analytical methods	Availability and use of in-house analytical methods	0 (0)	16 (88.9)	2 (11.1)
	Conducting system suitability test for compendia analytical procedures	0 (0)	9 (50.0)	9 (50.0)
Stability study	Availability of stability study programs	8 (44.4)	3 (16.7)	7 (38.9)
	Availability of stability study protocols	8 (44.4)	3 (16.7)	7 (38.9)
	Availability and use of written stability study procedures	8 (44.4)	1 (5.6)	9 (50.0)
	Availability of prospective and concurrent stability studies	8 (44.4)	1 (5.6)	9 (50.0)
Personnel management and training	Presence of personnel qualification program	2 (11.1)	13 (72.2)	3 (16.7)
	Presence of adequate and qualified personnel	9 (50.0)	7 (38.9)	2 (11.1)
	Availability and implementation of personnel training schedules	7 (38.9)	7 (38.9)	4 (22.2)
	Conducting induction training for new staff	6 (33.3)	5 (27.8)	7 (38.9)
	Presence of a continuous training program	7 (38.9)	0 (0)	11 (61.1)
	Provision of the refreshment training program	7 (38.9)	0 (0)	11 (61.1)
	Job descriptions and responsibilities are clearly stated	10 (55.6)	8 (44.4)	0 (0)
Manufacturing operations	Availability of SOPs for all manufacturing processes	8 (44.4)	10 (55.6)	0 (0)
	Availability of Batch Manufacturing Records	4 (22.2)	13 (72.2)	1 (5.6)
	Availability of Batch Packaging Records	2 (11.1)	7 (38.9)	9 (50.0)
	Use of Logbooks for major equipment with clear descriptors (name, calibration status, functionality, and usage entries)	2 (11.1)	12 (66.7)	4 (22.2)
Quality control (QC)	Availability of required analytical methods for QC operations	4 (22.2)	12 (66.7)	2 (11.1)
	Presence of SOPs for each analytical procedure	6 (33.3)	8 (44.4)	4 (22.2)
	Availability and use of SOPs for sampling and testing	8 (44.4)	6 (33.3)	4 (22.2)

	Presence of established specifications for all materials within QC	3 (16.7)	11 (61.1)	4 (22.2)
	Use of Certificate of Analysis for input materials supported with SOPs	3 (16.7)	10 (55.6)	5 (27.8)
	Implementation of GLP Principles in QC operations	4 (22.2)	11 (61.1)	3 (16.7)
Quality assurance (QA)	BMR and analytical records are reviewed and approved by QA	4 (22.2)	9 (50.0)	5 (27.8)
	Availability of SOPs for designing, revising, handling, and controlling documents	2 (11.1)	9 (50.0)	7 (38.9)
	Undertaking internal quality audits	2 (11.1)	9 (50.0)	7 (38.9)
	Presence of SOPs for rejection, reuse, and recall of products	7 (38.9)	8 (44.4)	3 (16.7)
	Availability of complaints handling system	4 (22.2)	12 (66.7)	2 (11.1)
	Proper storage of reference/retention samples	10 (55.6)	6 (33.3)	2 (11.1)
Sanitation and hygiene	Are all personnel undergo health examinations prior to employment and regularly afterwards	2 (11.1)	10 (55.6)	6 (33.3)
	All personnel are trained in personal hygiene practices	2 (11.1)	9 (50.0)	7 (38.9)
	Availability and use of SOPs on personal hygiene and hand washing	2 (11.1)	7 (38.9)	9 (50.0)
	All personnel are adequately on hygiene principles for critical operations (materials handling, operations, personnel flow, etc.)	5 (27.8)	9 (50.0)	4 (22.2)

Abbreviations: FI-fully implemented; PI-partially implemented; NI-not implemented.

Percent positive response (PPR) was calculated for each of the regulatory compliance dimensions where responses of only full implementation are considered as positive responses. Accordingly, the PPR was found to be high (44.4%) for documentation related to stability study followed by those related to personnel management (38.1%) as depicted in Fig 1.

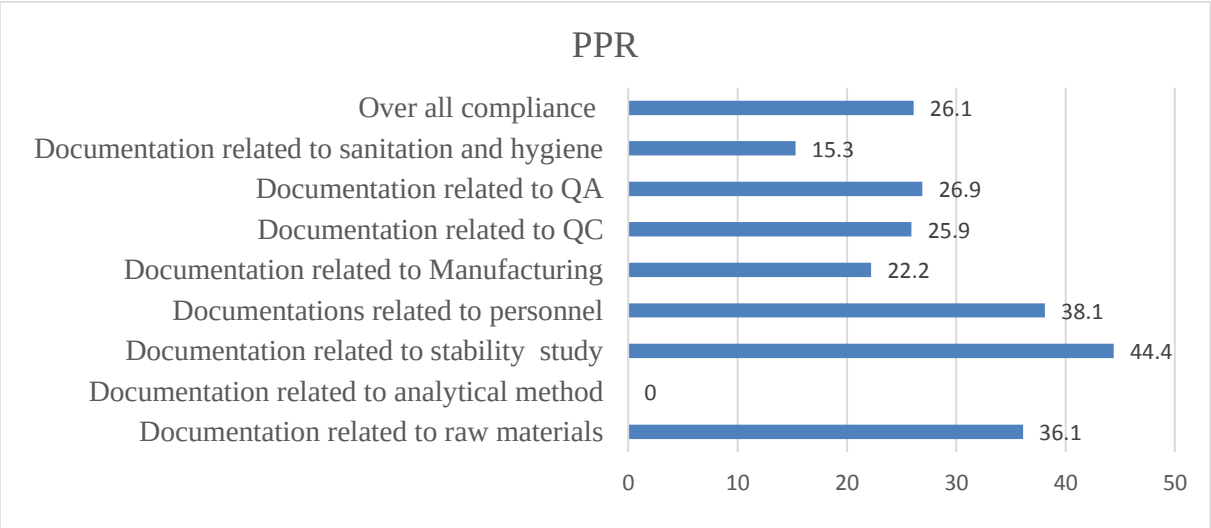

Figure 1. Percent positive response for regulatory compliance dimensions

The findings from the study revealed that competition from similar imported finished products, high production cost, lack of overall coordination among manufacturers and stakeholders, inadequate infrastructure, and inadequate government incentives are challenges to the local pharmaceutical manufacturers to implement quality management systems and adequately comply with regulatory requirements. In addition, challenges related to the regulatory system were reported by the manufacturers (Fig. 2).

The majority of the participants (88.9%) reported that locally manufactured products tend to be more expensive citing heavy reliance on imports for input materials, high cost of imported, resource constraints, erratic supply system, and inadequate infrastructure as contributing factors.

The presence of an adequate number and qualified staff is instrumental for the implementation of quality systems and compliance with regulatory requirements. In this regard, the study respondents reported different factors that contribute to the shortage of qualified experts including gaps from academic institutions in producing competent human resources needed by the pharmaceutical industry (83.3%), gaps related to training curricula for addressing the pharmaceutical industry needs (66.7%), lack of training facilities to train

technicians and equipment maintenance experts (55.6%), lack of effective consultancy services, particularly in technical know-how and R&D (44.4%), and high turnover of experienced staff (27.8%).

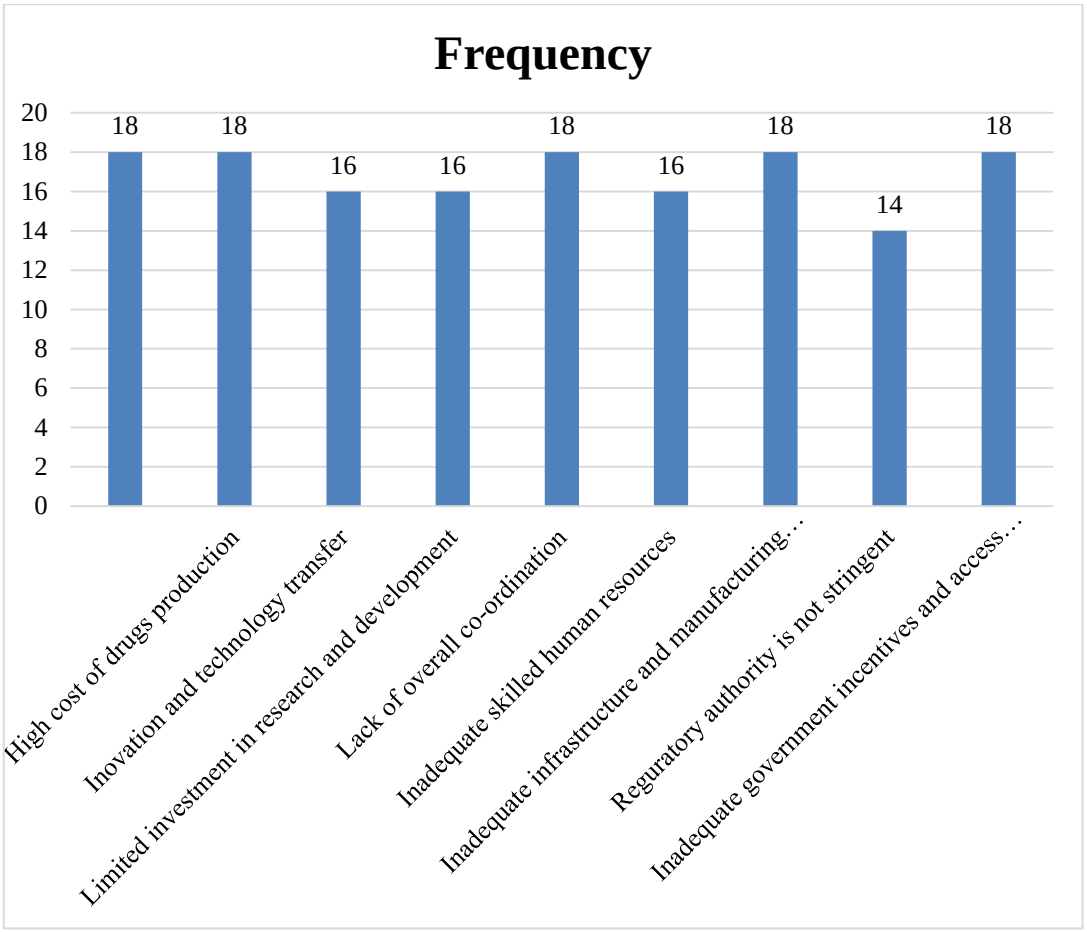

Figure 2. Challenges in implementation of quality systems and regulatory compliance

Table 4. Reported challenges in quality system implementation and compliance with regulatory requirements

Reported challenge	Response (N/%)
Limited capacity and expertise	16(88.9%)
Shortage of qualified personnel	14(77.8%)
Financial constraints and limited access to technology	14(61.1%)
Inappropriate premises and use of old technology	6(33.3%)
Weak regulatory law enforcement	5(27.8%)
Lack of effective coordination among the manufacturers	18(%)
Weak university-industry collaboration	14(77.8%)
Poor coordination among manufacturers, relevant government offices and development partners	13(72.2%)
Absence of regular inspection by regulatory bodies	1(5.6%)

Inadequate physical infrastructure was also reported by most of the respondents including utilities and equipment maintenance problems in (77.8%), power interruptions and high cost of running generators (72.2%), and very old manufacturing equipment and premises (38.9%) participants. Table 3 below presents recommended strategies by the respondents to strengthen the performance of small-scale local pharmaceutical manufacturing companies.

Table 5. Recommended strategies to strengthen the capacity and performance of local small scale pharmaceutical manufacturers

Proposed corrective measures	N(%)
Establishing a strong drug regulatory system to enforce the execution of GMP requirements and quality assurance systems.	11(61.1)
Timely correcting specific deficiencies by the companies	11(61.1)
Training of personnel on GMP	13(72.2)
Training and deploying skilled inspectors by the national regulatory authority	11(61.1)

Providing capacity-building support by sector stakeholders	8(44.4)

Inadequate access to financial loans and high-interest rates were also cited as important barriers to the development of the sector. In this regard, 83.3% of the respondents reported inadequate access to finance and gaps in comprehensive government incentives, about 2/3rd of the participants mentioned difficulties to access foreign currency, lack of policies to restrict products that can be sufficiently manufactured local (38.9%), and financial constraints by the manufacturing firms (16.7%).

4. Discussion

This study attempted to provide an insight into the implementation of regulatory requirements in small-scale local pharmaceutical manufacturing companies and the level of regulatory compliance. The findings from the study are discussed in consideration of practices in the companies, national regulatory policies, and international practices. Regulations and directives established for the regulation of pharmaceutical manufacturers and small-scale establishments require the implementation of GMP principles in core areas including raw materials, production processes, quality control activities, stability study, personnel management, and sanitation and hygiene. (11,12) The study revealed inadequate (below 50%) implementation of regulatory requirements by the small-scale manufacturing facilities in most of the essential GMP elements, particularly in the documentation and archiving. Half of the facilities didn't have Standard Operating Procedures (SOPs) for receiving and storage of raw materials; while 56% of the companies have no written SOPs for all manufacturing processes. None of the companies fully implemented regulatory requirements for system suitability tests for compendia analytical procedures, and only 44 % have written stability study procedures. Similarly, 50% of the companies could practice quality assurance activities, and only 22% of them could fully implement regulatory requirements in analytical method development and quality control

Pharmaceutical production is a complex undertaking demanding a large amount of finance, advanced technologies, objective research-based evidence, and collaborative effort among sector stakeholders; which otherwise may result in health and economic risks. (13) As they are essential lifesaving products, pharmaceuticals are equally life-threatening if their safety, efficacy, and quality could not be consistently ensured. In consideration of these important attributes, pharmaceutical production requires well-characterized products and formulation; dependable quality control and quality assurance system; an adequately trained and qualified workforce; adequate and sustainable financing; and precise standards with stringent regulatory follow-up. (13, 14)

For small-scale pharmaceutical manufacturing facilities, particularly those in developing countries, limited exposure and expertise in the sector; lack of adequate expertise, training, and finance for quality systems implementation, inadequate adoption of good manufacturing practices to meet regulatory standards; limited capacity for the adoption of technology, weak collaboration with sector stakeholders are some of the contributing factors for the low level of quality systems implementation by the companies. (15, 16) Even though such manufacturing facilities produce a limited number of products mainly for minor illnesses in conventional dosage forms; and other healthcare consumables, the potential risks still exist. Lack of regular and effective regulatory oversight and weak regulatory law enforcement can also contribute to the poor implementation of quality systems and regulatory requirements. Similar challenges have been reported even for large-scale pharmaceutical manufacturers in Ethiopia and other countries. (17-19) Along with close regulatory oversight to ensure the implementation of minimum requirements, providing integrated capacity-building support by responsible stakeholders can have a significant contribution.

The study attempts to identify major challenges hindering the effort for compliance to regulatory requirements established by the national regulatory authority. Accordingly, inadequate physical infrastructure, lack of advanced technology for production and quality control, shortage of technical expertise, limited investment in research and formulation development, high competition from low price imported products, weak coordination among manufacturers and stakeholders, inadequate government incentives, financial constraints, limited access to foreign currency, and high production cost because heavy reliance on import for input materials are some of the challenges reported by study participants. Similar challenges have also been reported in other countries. (20,21)

Small scale and startup companies, if effectively supported with enabling policy frameworks, technology transfer, and capacity building, can be transformed into large-scale industries that can contribute to improving access to essential medicines and other healthcare supplies. From the study, the issue of innovative product development and technology transfer was reported as a major challenge by the companies. Experts in the sector recommend that knowledge interactions among firms, public research institutions, policy formulators, and technology incubation firms are key elements for the success of small-scale pharmaceutical production facilities. (22, 23) The firms have a very instrumental role in healthcare by supplying essential medical supplies, hospital consumables, and extemporaneous pharmaceutical products. By virtue of their properties and their clinical use, the products require careful attention to quality by manufacturers regulators, health professionals, and end-users. Implementation of standard quality systems as stipulated under the national regulatory framework has a significant contribution to reducing health risks, and collaborative effort is required to support the firms. Establishing a strong network among the industry, academic and research institutions, and other government institutions with clear policy platforms substantially reduces the reported challenges and provides continuous capacity-building schemes for the local companies. (24)

The primary responsibility is ensuring the safety and quality of their products and complying with regulatory requirements is the manufacturers. In addition to investing in physical infrastructure and quality systems; establishing effective leadership; implementing clear strategies for product development, technology acquisition, human resource development, and marketing; forging effective collaboration with stakeholders should be executed. Similar strategies have proved successful experiences in other countries. (25,26)

Limited capacity and operating under a low economy of scale, compounded by increasing prices for the import of input materials and a sluggish logistics system do have a significant influence on the growth of the companies. Establishing arrangements for pull procurement and logistics services and business consolidation can help the companies somehow alleviate the increasing pressure from imported low price products as has been recommended by experts. (13,27)

Strong regulatory control is critical for protecting the public from unsafe and poor-quality products. Along with ensuring the efficacy, safety, and quality of medicines circulated in the market, competent regulatory authorities can provide support for local manufacturers and facilitate access to affordable essential medicines. The study participants reported that weaknesses in the inspection of manufacturers and importing firms, limited capacity and regulatory law enforcement, and shortage of experienced staff are major influencing factors for the performance of the regulatory system. Previous studies reported that regulatory authorities in African countries have similar challenges to effectively undertaking core regulatory functions. (1, 28)

In addition to regulating local manufacturers and importers, strengthening the regulatory system is essential to prevent the circulation of counterfeit and substandard products in the light of increasing risk and the porous nature of the region. Because of the cross-border nature of the pharmaceutical business and regulatory functions, initiatives for harmonizing regulatory standards and functions have been started in different regions including Africa. (29, 30) Such initiatives can offer opportunities to improve capacity, performance, and collaboration of the regulatory authority which in turn can support the local manufacturers in technical capacity building.

5. Conclusion

The study demonstrated that level of regulatory requirements implementation in the local small-scale pharmaceutical manufacturers is far below the minimum standard set by the national regulatory authority. Of the total regulatory requirements, only 26.1% could be implemented by the manufacturers. Important gaps were reported particularly in materials management, production operations, quality control, and sanitation and hygiene. Inadequate physical infrastructure, lack of dependable quality systems, lack of technical expertise, high competition from low price imported products, inadequate support from stakeholders, and financial constraints were identified as major limiting factors in implementing standard quality and regulatory requirements by the manufacturers. Limited regulatory oversight and weak enforcement practice of regulatory legislations have also been reported as contributing factors. Considering the important role of the local firms in healthcare, and the potential health risks associated with product quality defects, the respective companies, regulatory bodies, and sector stakeholders should collaboratively support the implementation of quality systems and regulatory standards.

From the total regulatory requirements set related to raw materials, 36.1% requirements were implemented, requirements related to stability study 44.4% were implemented, requirements related to personnel 38.1% were implemented, requirements related to manufacturing operation 22.2%r were implemented, requirements related to QC 25.9 were implemented, requirement related to QA 26.9, requirement related to sanitation and hygiene 15.3% were implemented.

Finally, the major challenges faced by the local pharmaceutical manufacturer industry in the implementation of regulatory requirements were highlighted and discussed, significant challenges: including human resource capacity constraints, limited access to foreign currency, and raw material procurement difficulties are some of the major challenges.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Declarations

Ethical consideration

The research has the ethical clearance from the School of Pharmacy ethical review committee (**Reference No**. **ERB/SOP/95/04/2019**) and a letter from EFMHACA. Permission from each small-scale pharmaceutical manufacturing company was also obtained before cascading the research. Verbal consent was also obtained from the study participants after explaining the purpose of the study, the benefit of participating in the study, why and how they were selected for the study, and what was expected of them. Participants were assured about the confidentiality of the information they provide in the course of the study and were informed that personal and pharmaceutical company identifiers will not be used. Because of confidentiality, the issue with respect to regulatory compliance of the pharmaceutical company, code was used for each company, and all information is secured and used only for research purposes.

Authors' contributions

This work is part of the MSc thesis of WK, GB is the principal supervisor of the study, and TM is the co-supervisor of the study, MM improved the manuscript by extensive editing, correcting, and commenting on the manuscript.

References

1. World Health Organization. Assessment of medicines regulatory systems in sub-Saharan African countries. An overview of findings from 26 assessment reports. Geneva: WHO; 2010.
2. SESRIC. Pharmaceutical Industry in OIC Member Countries: Production, Consumption, and Trade, Statistical Economic and Social Research and Training Centre for Islamic Countries (SESRIC), Organization of Islamic Cooperation: Kudüs Caddesi No 9. 06450 Çankaya, Ankara, Turkey [Internet]. 2011 [cited 2022 Feb 22]. Available from:
   Available from:
   https://www.sesric.org/files/article/433.pdf
3. Amara AH, Aljunid SM. Local pharmaceutical production as means to improve access to essential medicines in developing countries. International Journal of Pharmacy and Pharmaceutical Sciences. 2012;4(4):233-40.
4. Hodel R. Emerging Pharmaceutical Infrastructure in Sub-Saharan Africa. In Chemistry as a Second Language: Chemical Education in a Globalized Society. American Chemical Society; 2010.p.159-180
5. Olliaro PL, Vijayan R, Inbasegaran K, *et al*. Drug studies in developing countries. Bull World Health Organ. 2001; 79(9):894.
6. Masupye EM, Suleman F, Govender T. Investigating extemporaneous compounding practices in the Polokwane tertiary hospital pharmacies in South Africa-a pilot study. African Journal of Pharmacy and Pharmacology. 2015 Dec 29;9(48):1099-105.
7. Mohiuddin AK. Extemporaneous compounding: cautions, controversies, and convenience. Innovative Journal of Medical and Health Science. 2019;9(1):252-64.
8. Union A. Report of the 8th session of the Africa population commission; 15-16 Sept 2011.
9. EFMHACA. Small scale medicine establishment directive, Food, Medicine and Health Care Administration and Control Authority of Ethiopia (FMHACA), Addis Ababa; 2014a.
10. Bartsch S. The global fund to fight AIDS, tuberculosis, and malaria. In Global health governance and the fight against HIV/AIDS. London: Palgrave Macmillan; 2007.p. 146-171
11. EFMHACA (2014b). Good Manufacturing Practice Guideline for Pharmaceutical Products: Main Principles, Food, Medicine and Health Care Administration and Control Authority of Ethiopia (FMHACA), Addis Ababa; 2014b
12. Harmonization R. Prequalification of Medicines Programme. WHO Drug Information. 2010;24(1).
13. UNDP. How local production of pharmaceuticals can be promoted in Africa: the case of the United Republic of Tanzania. United Nations Development Programme [Internet]. Dar es Salaam: UNDP; 2016 [cited 2022 Apr 22]. Available from:
    https://adphealth.org/upload/resource/Tanzania_Local_Production.pdf.
14. Njeri GM. An investigation of factors affecting work life balance in non-governmental organizations (NGOs): A case of Management Sciences for Health (MSH) (Doctoral dissertation) [Internet]. Africa: United States International University; 2014 Aug 30 [cited 2022 Apr 21]. Available from:
    http://erepo.usiu.ac.ke/11732/78
15. Iyer PK. Structure and Performance of Small and Medium Scale Pharmaceutical Firms. India, Science and Technology. [Internet]. 2008 Mar 15 [cited 2022 Apr 27]. Available from::
    https://ssrn.com/abstract=1752125
16. Conway M, Holt T, Sabow A, Sun IY. Should sub-Saharan Africa make its own drugs; 2020.
17. Narsai K, Williams A, Mantel-Teeuwisse AK. Impact of regulatory requirements on medicine registration in African countries–perceptions and experiences of pharmaceutical companies in South Africa. Southern med review. 2012 Jul;5(1):31.
18. Gebre-Mariam T, Tahir K, Gebre-Amanuel S. Bringing industrial and health policies closer: reviving pharmaceutical production in Ethiopia. Making Medicines in Africa. London: Palgrave Macmillan; 2016.p. 65-84
19. Rasheed H, Hoellein L, Bukhari KS, Holzgrabe U. Regulatory framework in Pakistan: situation analysis of medicine quality and future recommendations. Journal of Pharmaceutical Policy and Practice. 2019 Dec;12(1):1-5.
20. Ekeigwe AA. Drug manufacturing and access to medicines: the West African story. A literature review of challenges and proposed remediation. AAPS Open. 2019 Dec;5(1):1-5.
21. Tauqeer F, Myhr K, Gopinathan U. Institutional barriers and enablers to implementing and complying with internationally accepted quality standards in the local pharmaceutical industry of Pakistan: a qualitative study. Health policy and planning. 2019 Jul 1;34(6):440-9.
22. Kilama WL. The 10/90 gap in sub-Saharan Africa: resolving inequities in health research. Acta tropica. 2009 Nov 1;112:S8-15.
23. Fromhold-Eisebith M, Schartinger D. Universities as agents in regional innovation systems. Evaluating patterns of knowledge-intensive collaboration in Austria. In The emergence of the knowledge economy. Springer, Berlin, Heidelberg; 2002.p. 173-194
24. Rasheed H, Hoellein L, Bukhari KS, Holzgrabe U. Regulatory framework in Pakistan: situation analysis of medicine quality and future recommendations, J of Pharm Policy and Pract. 2019; 12 (23):1-15
    doi.org/10.1186/s40545-019-0184-z
25. Kruss G. Balancing old and new organisational forms: changing dynamics of government, industry and university interaction in South Africa. Technology Analysis & Strategic Management. 2008 Nov 1;20(6):667-82.
26. Siyanbola WO, Egbetokun AA, Oluseyi I, Olamade OO, Aderemi HO, Sanni M. Indigenous technologies and innovation in Nigeria: opportunities for SMEs. American Journal of Industrial and Business Management. 2012; 2(2).
27. Collier P. Economic causes of civil conflict and their implications for policy. Department of Economics, Oxford University; April 2006.
28. Dube-Mwedzi S, Kniazkov S, Nikiema JB, Kasilo OM, Fortin A, Tumusiime P, Mahlangu GN, Ndomondo-Sigonda M. A rapid assessment of the National Regulatory Systems for medical products in the Southern African Development Community. Journal of Pharmaceutical Policy and Practice. 2020 Dec;13(1):1-0.
29. Ndomondo-Sigonda M, Miot J, Naidoo S, Dodoo A, Kaale E. Medicines regulation in Africa: current state and opportunities. Pharmaceutical medicine. 2017 Dec;31(6):383-97.
30. Harmonization R. Prequalification of Medicines Programme. WHO Drug Information, Geneva. 2010;24(1).