Reducing the Burden of Inspections on Pharmaceutical Manufacturers by Regulatory Authorities in Benin City, Nigeria

Joseph Ali

Esther Itua

Zita Ekeocha

Kari Clase

Stephen Byrn

Reducing the Burden of Inspections on Pharmaceutical Manufacturers by Regulatory Authorities in Benin City, Nigeria

J. Ali[1], E. Itua[2], Z. Ekeocha[3], S. Byrn[4], K. Clase[5]

ABSTRACT

In Nigeria, pharmaceutical manufacturing is regulated by the Pharmacists Council of Nigeria (PCN) and the National Agency for Food and Drug Administration and Control (NAFDAC). The PCN Act gave the regulatory authority the mandate to register all pharmaceutical premises. With the later creation of NAFDAC to regulate drugs, comes the dual regulatory authority on those premises by both government agencies who carry out Good Manufacturing Practice (GMP) inspections in the process of carrying out their mandates. Dual regulatory authority and inspections puts a considerable inspection burden on the manufacturers and even the regulators. This study examined the inspection tools used by each agency, the acts setting them up, as well as best practices around the world on inspections and regulatory frameworks. The goal was to identify regulatory practices that lessen the burden of inspection on pharmaceutical manufacturers and regulators. A review of the agencies' inspection tools showed both PCN and NAFDAC utilize the World Health Organization (WHO) guidelines and templates on inspections. The primary function of PCN is the regulation of pharmacy and pharmacy practice with added responsibility to register and certify premises for pharmaceutical manufacturing purposes. NAFDAC's primary role, on the other hand, is to regulate pharmaceutical products. Both PCN and NAFDAC carry out this regulatory function on pharmaceutical manufacturing premises through Good Manufacturing Practice (GMP) inspections. This study showed an overlap in the agencies' functions with respect to the inspection of pharmaceutical manufacturing premises before certification, thus creating a duplication of regulatory functions. Inter-agency collaboration would be of great value to lessen the burden on the manufacturers from frequent GMP inspection visits.

Keywords

Keywords: inspections, burden, pharmaceutical manufacturing, regulatory agency, Good Manufacturing Practice

[1] ali26@purdue.edu; Biotechnology Innovation and Regulatory Science (BIRS) Center; Agricultural and Biological Engineering, Purdue University
[2] ituaesther@gmail.com; National Agency for Food and Drug Administration and Control
[3] zekeocha@purdue.edu; Medical Missionaries of Mary; Biotechnology Innovation and Regulatory Science (BIRS) Center, Purdue University
[4] sbyrn@purdue.edu; Biotechnology Innovation and Regulatory Science (BIRS) Center; Industrial and Physical Pharmacy, Purdue University
[5] kclase@purdue.edu; Biotechnology Innovation and Regulatory Science (BIRS) Center; Agricultural and Biological Engineering, Purdue University

INTRODUCTION

Inspections indicate “careful analysis and assessment implying scrutiny, quantification, trial, estimating, and contrasting of equipment or things. An inspection ascertains if the material or item is in appropriate amount and state, or if it complies to the relevant or defined stipulations” (“Inspections,” 2010). Inspections are generally in three categories, which include receiving inspection, in-process inspection, and final inspection.

Inspections of facilities by regulatory authorities refers to the scrutiny accorded such facilities for the purpose of compliance to pre-established standards. Inspections can also be carried out by the firm prior to visit by the regulatory authorities, which is known as self-inspection. A neutral individual or group of experts can also carry out inspections by review of quality system of a company in conforming with the standards issued by the International Organization for Standardization (ISO 9000-9004). Inspections can also be used to inform of an audit of the producer or supplier by authorized agent of the customer.

GMP is a system for guaranteeing that products are constantly produced and controlled corresponding to quality standards. GMP is put in place by regulation to decrease the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product. (International Society for Pharmaceutical Engineering, n.d).

GMP can only be ensured by inspections which is carried out either internally or externally by auditors or government regulatory authorities. The function of the regulatory authorities is to enforce adherence to GMP guidelines by the pharmaceutical manufacturers.

According to the World Health Organization (WHO), “the main objective of inspecting pharmaceutical manufacturing facilities is to enforce GMP compliance or to provide authorization for the manufacture of specific pharmaceutical products, usually in relation to an application for marketing authorization.’’ Inspection is also used to monitor the quality of pharmaceutical products in distribution channels from point of manufacture to delivery to the recipients (World Health Organization, 2007).

In conducting a regulatory inspection, the inspectors and representatives of the company have a pre-inspection meeting at the facility to be inspected where the purpose of the inspection is made known by the regulator. Depending on the objective of the inspections, the inspection type could be routine, concise, special, review of quality system, or re-inspection. In all of these types of inspections, the manufacturer is involved and prepares for the regulatory visits for the purpose of the exercise.

In Nigeria, this GMP inspection is carried out by two separate regulatory agencies, each having its own mandate over the manufacturer. However, both carry out the same GMP inspection. A scheduled inspection visit by the Pharmacists Council of Nigeria (PCN) inspection team to a facility takes an average of three days for the team to prepare, in terms of traveling and other logistics, and a minimum of five hours on the floor of the factory being visited. A routine inspection is carried out once in two years while compliance visits can be carried out at any time within routine outings. During such visits, the facility “practically shuts down” as the attention of all key personnel in such facilities is required by the inspection team and most of the staff are anxious about the presence of federal inspectors.

Inspection of a pharmaceutical manufacturing facility by the PCN is coordinated by the head office of the agency. The inspection team, which is usually led by the head of the department of Inspection and Monitoring of PCN, travels from the head office and is joined by the zonal inspectors to the facility. Thus, significant preparation and resources are required.

Similar guidelines for the routine inspection of pharmaceutical manufacturers is carried out by The National Agency for Food and Drug Administration and Control (NAFDAC). NAFDAC also carries out compliance inspections anytime within the once in two years routine outing to the facilities

On average, the manufacturers expect visits from one of the two regulatory authorities every year and must prepare separately for such visits. The department of Drug Evaluation and Research (DER) is responsible for carrying out GMP inspections for NAFDAC.

The Pharmacists Council of Nigeria is a Federal Government Agency established by an act of parliament (Pharmacists Council of Nigeria Act, 2004). The agency is assigned the obligation of regulating and controlling the education, training, and practice of pharmacy in all perspectives and divergence. The PCN has the broad mandate, amongst others, of:

- ascertaining the quality and excellence of knowledge and skills to be obtained by individuals seeking to become members of the pharmacy profession and reassessing those qualities from time to time as situations may require;
- securing, in accordance with the provisions of the Act, the founding and maintenance of registering individuals entitled to practice as

members of the profession and the publication from time to time, and lists of those persons;

- reviewing and preparing from time to time, a statement as to the code of conduct which the council considers desirable for the practice of pharmacy;
- the council inspects, approves, and licenses premises where pharmaceutical activities take place including pharmaceutical manufacturing, importation, mega/state drug distribution centers, distribution, wholesale and retail premises, hospital pharmacies, and patent and proprietary medicines vendors licenses;
- registering and issuing annual permits to Pharmacy Technicians;
- organizing Mandatory Continuing Professional Development (MCPD) for Pharmacists (Pharmacists Council of Nigeria Act, 2004).

All areas of pharmaceutical practices in Nigeria are under the control of the Pharmacists Council of Nigeria. The act makes the registration of premises in Nigeria prior to starting of a pharmaceutical firm possible. The Act enacts the PCN ("the Council"), as the organization with the exclusive duty of registering, keeping track of and supervising all retail, wholesale and manufacturing outlets of pharmaceuticals. The Council in practice of the authority bestowed upon it by the Act in section 1 and 24, created regulations steering the registration of premises.

Registration of Pharmaceutical Premise

The Registration of Pharmaceutical Premises Regulation of 2005, which is a PCN guideline, makes registration of fresh pharmaceutical premises and renewal of existing outlets possible. It makes provision that in a situation where an outlet strives to be enrolled as a retail drug store, the corporation shall be solely owned by a registered pharmacist or in association with other registered pharmacists.

Where drugs and medicines establishments engaged in large-scale distribution and importation of drugs, poisons and devices, there shall be at least one registered pharmacist on the board of directors of the firm and this shall be accomplished under the direct supervision and management of a superintendent pharmacist.

In a situation where the main objective of the corporation is manufacturing, there shall be at least one registered pharmacist on the board of directors of the company. The business shall be accomplished under direct personal and management of a superintendent pharmacist.

"The Inspection, Location and Structure of Pharmaceutical Premises Regulations 2005," which is a PCN guideline, provides for an inspectorate unit. This unit is made up of registered pharmacists delegated as pharmaceutical inspectors, chosen by the council to go into any drug store or firm and inspect to ensure required conformity with the outline of the regulations.

a) The inspection**,** Location and Structure of Pharmaceutical Premises Regulations of the PCN make provisions for the siting of premises such that it shall not be situated in parking garages, surroundings proximal to a location where mercantile undertakings and ventures are existing and flourishing or marketplaces, including booths and roadside stalls.

b) It also provides that any premises encompassed or canopied entirely by an expanding market or standing nearby to it shall be shifted to some other satisfactory place two years succeeding official notification to do so by the Council.

c) Premises inside shopping centers shall not be more than three and they shall be skillfully spread out.

d) Pharmaceutical premises shall be situated not less than 200 meters from another pharmaceutical premises.

Where the premises sought to be registered as a pharmaceutical manufacturing, the regulation requires the corporation to forward the following additional requirements as part of the application process:

a) list of items to be produced;

b) list of equipment for manufacturing and quality control;

c) list and sources of suppliers of raw and packaging materials;

d) standard operating procedures (SOP);

e) factory layout;

f) production flow chart;

g) water source and treatment facilities;

h) water analysis report (raw and treated water);

i) list of qualified staff showing qualifications and duty;

j) organogram;

k) disposal of poison records;

l) prescribed inspection fees in bank draft payable to PCN;

m) product licenses for all products (in the course of regular inspections); and

n) list of all distributors and distribution records (in the course of routine surveillance).

The National Agency for Food and Drugs Administration and Control (NAFDAC) is also a Nigerian Government Agency established by *Act Cap N1 LFN 2004* and assigned with the authority of regulating and controlling the importation, exportation, manufacture, advertisement, distribution, sale and use of foods, drugs, cosmetics, medical devices, bottled water and chemicals.

The complementary role of NAFDAC in relation to pharmaceutical regulations includes:

a) assessment and registration of pharmaceutical products;

b) post market surveillance and risk analysis of products;

c) control of product shipping-in and shipping-out; and

d) regulation of product promotion and public education.

The agency, in exertion of its authority bestowed upon it by the Act in sections 5 and 30, made the following regulations known as “Drugs and Related Products Registration Regulation” (2019). The regulations apply to the registration of drugs and related products manufactured, imported, exported, advertised, sold, distributed, or used in Nigeria and prohibits any of the products from being manufactured, imported, exported, advertised, sold, distributed, or used in Nigeria unless in accordance with this regulation (Drugs and Related Products Registration Regulations, 2019). The regulation requires that a completed application form is submitted with relevant supporting documents which shall:

a) contain the names of the product to be manufactured;

b) be accompanied by proof of payment of the prescribed application fees (registration, etc.) (Act cap F33 LFN 2004).

Section 15 of the NAFDAC regulation gives the power to seal. “That the Agency shall have power to seal up any premises used or being used in connection with any offence under these Regulations until such time as the regulated product is removed or such reasonable time as the Minister may determine” (Act Cap N1 LFN 2004).

A pharmaceutical manufacturing firm intending to produce drugs in Nigeria is expected to apply for a pre-production inspection by NAFDAC and must have at least a registered pharmacist on the board of the company. It must also employ a superintendent pharmacist duly registered with the PCN. In addition, the manufacturing premises should be registered with PCN. According to the Pharmacists Council of Nigeria, there are 132 registered pharmaceutical manufacturing facilities in Nigeria in year 2018.

There are seven government regulatory agencies of relevance to the pharmaceutical manufacturing sector each having its mandate, as shown in Table 1.

Table 1
Regulatory Bodies of Relevance to Pharmaceutical Manufacturers in Nigeria

Regulatory body	Mandate
Corporate Affairs Commission (CAC)	Company registration
Federal Ministry of Commerce	Brand name and trademark approval
Nigerian Export Promotion Council (NEPC)	Export regulated products
National Health Insurance Scheme (NHIS)	Health Insurance (Medicines)
Pharmacists Council of Nigeria (PCN)	Registration of premises.

National Agency for Food and Drug Administration and Control (NAFDAC)	Registration of pharmaceutical products.
National Office for Technology Acquisition and Protection (NOTAP)	Intellectual property rights and patents.

The pharmaceutical sector in Nigeria is essentially regulated by two agencies of the Federal Ministry of Health, namely PCN and NAFDAC. The PCN regulates the training and practice of pharmacy, including the development of basic pharmacy curricula for degree programs and mandatory continuing education programs. It also regulates all premises where pharmacists practice their profession viz-manufacturing premises, dispensing pharmacies, and drug warehouses. Thus, PCN inspects premises to ensure compliance with GMP and approves the premises for pharmaceutical manufacturing.

Alternatively, NAFDAC regulates all drug products and substances, chemicals, bottled water, and packaged food. NAFDAC also inspects the pharmaceutical manufacturing premises to ensure that the facilities are satisfactory for production of the specific products. The mandates of the two regulatory agencies requires that GMP inspection of a pharmaceutical facility is carried out before certification and or marketing authorization can be issued by each agency and this is the reason for dual inspection of facilities in Nigeria.

The government made a promise to its citizens through the National Drug Policy (2005) and set a target for 70% (in volume) of the country's demands for medicines to be met by local drug manufacturers by the year 2008. Consequently, government policies support local production of essential medicines in accordance with the NDP. However, the drug manufacturers have complained that the ease of doing business has not been encouraged by the government agencies charged with the responsibility of regulation, hence impeding on the set target.

There are regulatory frameworks and practices in other countries on how pharmaceutical manufacturing is regulated that could provide more insights to this study. Below are frameworks and practices from selected countries across the globe.

West Africa-Ghana

Ghana's pharmaceutical sector is regulated by two regulatory government bodies, namely the Pharmacy Council of Ghana and the Food and Drugs Authority Ghana (FDA Ghana), formerly Food and Drugs Board (FDB). The FDA Ghana is an agency under the Ministry of Health and has the mandate to inspect, certify, and distribute all foods, as well as drugs, properly. The agency was established in August 1997 under the Food and Drugs Law 1992, PNDC Law 305B. The FDA Ghana is responsible for inspection of factories and warehouses while the Pharmacy Council inspects and registers pharmacies and drug dispensing outlets. The difference between the Nigerian Structure and that of Ghana is that inspection and registration of the manufacturers is carried out by only one of the agencies – FDA Ghana, in this case.

East Africa-Kenya

The Pharmacy and Poisons Board (PPB) of Kenya is the sole Medicine Regulatory Authority (MRA). PPB is responsible for inspection, registration, licensing, market control, pharmacovigilance, medicines advertisement and promotion, as well as clinical trials of drugs, in the Kenyan pharmaceutical manufacturing industry.

South Africa-Botswana

In Botswana, the Drug Regulatory Unit (DRU), under the Ministry of Health, is the Botswana Medicine Regulatory Agency established by the government for the purpose of pharmaceutical sector regulation. The responsibility is to regulate, approve, and register drugs and medicines to ensure standards of safety, efficacy, and quality. The DRU is the sole authority that inspects and registers pharmaceutical manufacturing facilities, as well as controls imports and clinical trials.

North Africa-Egypt

The pharmaceutical country profile of Egypt indicates that the sole Medicine Regulatory Authority in the country is the Egyptian Drug Authority (EDA) under the Ministry of Health. The agency's functions include inspection, marketing authorization, import control, licensing, market control, quality control, pharmacovigilance, medicine advertisement and promotion, clinical trials control, and registration of all pharmaceutical premises including manufacturers.

North America-United State of America

In the United States, the Department of Health and Human Services (DHHS) is responsible for pharmaceutical regulation. The US Food and Drugs Administration (FDA) is an independent agency established by the Food, Drug and Cosmetic Act (FDCA) of 1938 to regulate the importation, manufacture, distribution and sale of drugs in the United States. The FDA act empowers the agency to carry out inspections of pharmaceutical manufacturing facilities as part of the regulatory function.

Asia-Japan

The Pharmaceuticals and Medical Devices Agency is the Japanese government organization similar in function to the US FDA. Among other things, the agency is tasked with the following:

- Drug and medical device testing:
- Scientific review of market authorization applications based on Japanese pharmaceutical law;
- Advice in clinical trials or in the preparation of dossiers for the registration procedures (New Drug Applications (NDA);
- Inspection and conformity assessment of Good Clinical Practice (GCP), Good Laboratory Practice (GLP) and Good Practice Systems and Programs (GPSP);
- Auditing of manufacturers to ensure they conform to Good Manufacturing Practice (GMP).

European Union

The European Union's (EU) legal framework for pharmaceuticals is aimed at ensuring a high level of protection of public health. It is based on the principle that placing of a medicine on the market is subject to the granting of a marketing authorization by the competent authorities.

The European Medicines Agency (EMA) is the body responsible for the scientific evaluation of centralized marketing authorization applications of medicines. Once granted by the European Union (EU) the centralized marketing authorization is valid in all EU member states (with the exception of UK exiting from the EU), Iceland, Norway, and Liechtenstein.

The Community codes for veterinary and human medicines are set out in Directive 2001/82/EC and Directive 2001/83/EC respectively. They provide the legal framework for the authorization, manufacture and distribution of medicines in the EU.

Australia

In Australia, pharmaceutical sector regulations are under the Therapeutic Goods Administration empowered by the Therapeutic Goods Act of 1998 and the Therapeutic Goods Regulations. These regulations are responsible for the quality, safety and efficacy, and timely availability of medicines and medical devices in Australia. The agency is under the Australian Department of Health and has nine different statutory expert committees it may call upon to obtain independent advice on scientific and technical matters including:

a. Advisory Committee on Biologics (ACB);
b. Advisory Committee on Complementary Medicines (ACCM);
c. Advisory Committee on Medical Devices (ACMD);
d. Advisory Committee on Non-prescription Medicines (ACNM);
e. Advisory Committee on Prescription Medicines (ACPM);
f. Advisory Committee on the Safety of Medical Devices (ACSMD);
g. Advisory Committee on the Safety of Vaccines (ACSOV);
h. Advisory Committee on the Safety of Medicines (ACSOM);
i. Therapeutic Goods Committee (TGC)-advises the Minister on standards for therapeutic goods, including labelling and packaging and on principles to be observed in the manufacture of therapeutic goods for use in humans.

Brazil

Brazil, the largest country in South America, has become the largest pharmaceutical market in the emerging world. The Brazilian Health Surveillance Agency (Agentia Nacionale de Vigilancia Sanitaria-(ANVISA) is the country's health regulatory agency linked to the Ministry of Health, part of the Brazilian National Health System (SUS) as the coordinator of the Brazilian Health Regulatory System. ANVISA's role is to promote the protection of the population's health by executing sanitary control of the production, marketing, and use of products and services subject to health regulation, including related environments, processes ingredients and technologies, as well as the control in ports, airports and boarders. ANVISA is the sole agency for the regulation of pharmaceuticals in Brazil and it also carries out inspections of manufacturing facilities and certifies them.

The purpose of this project was to examine the individual act of parliament setting up the Pharmacists Council of Nigeria and the National Agency for Food and Drugs Administration and Control, the two main regulatory agencies of the pharmaceutical sector in Nigeria. The aim was to find areas of functional overlaps. The project also reviewed the GMP inspection tools used by both agencies with a view to explore areas that lead to duplication of functions by the two agencies. Further reviews of regulatory frameworks and practices across selected countries were made. The review was to observe how the pharmaceutical manufacturing sector is regulated in such countries. The objective here was to recommend to the management of both agencies on the need to consider some best practices that could improve the Nigerian system. Such improvement

would ultimately lead to improvement in service delivery by the manufacturers such as increased and timely production of medicines of which delays had been attributed to delays in regulatory inspections and approvals over time.

Regulatory inspection of pharmaceutical manufacturing facilities is a vital element of good manufacturing practice compliance as far as drug control is concerned. Harmonization of inspections and supervision by regulatory authorities to avoid different interpretations by manufacturers is equally important in ensuring standards of quality of pharmaceutical products. Recent studies in Pakistan identified lack of adequate regulatory inspection as the reason for some pharmaceutical manufacturing facilities operating under different GMP standards and interpretations. The operation of these companies was reported as being a failure of the national drug regulatory authority to carry out effective inspection and supervision. Some of the challenges identified by the study were lack of access to quality products which was attributed to inability of the regulatory authority to ensure manufacturers comply to and implement quality standards. The need for global harmonization of quality standards and regulatory supervision was emphasized (Tauqeer, Myhr and Gopinathan 2019). In this example, regulation of pharmaceutical manufacturing is carried out by a single government regulatory agency who carries out inspection and directives from the regulator to the manufacturer are from one source, hence lesser burden as against two government regulatory agencies having to inspect the facilities separately before certification.

In a recent study on impact of regulatory requirements on medicine registration in Africa, it was reported that GMP inspection by regulatory agencies is a barrier to the registration and supply of medicines, which includes high fees of GMP inspections and other regulatory activities (Narsai, Williams and Mantel-Teeuwisse 2012).

Reducing the burden of inspections on regulators is also important due to the growing number of facilities to be inspected and the limited resources of the regulatory agencies. The risk-based approach initiative on inspections by the US FDA is worth mention here, whereby an FDA's certified agent carries out the inspection on behalf of the FDA on selected 'low priority' inspections. This is to free time and space for the FDA so as to concentrate on 'high priority' facilities and enforcement activities to ensure timely registration and release of products to the market. (National Academies Press (US), 2010).

The National Research Council Committee on the review of FDA's roles in a recent report emphasized the need for reform. The inspection is concise and targeted at areas with higher risk to the public as against auditing of the entire facility. Such risk based inspection system helps in resource management. To buttress the setting up of such a system, an external task force should review the possible legal and cultural barriers to smooth-running inspections and amend the *Investigations Operations Manual* in order to obtain effectiveness and preservation of the public health. As a precondition for a risk-based inspection technique, the FDA needs to update its GMPs, as well as those for medicated animal feed, at the moment and subsequently as needed. (Scott, J. 2009).

Due to the importance of drug as a consumer product, its regulation is almost exclusive to federal governments across the globe. Pharmaceutical firms are required to conduct separate tests, submit separate applications and meet distinctive criteria to enter each national market. However, recent clamor for globalization of pharmaceutical regulations has resulted in national regulatory agencies beginning to cooperate more closely with one another. The European Union has established a centralized drug approval system, the United States Food and Drug Administration has become more willing to cooperate with its foreign counterparts, and the United States, the EU and Japan have made substantial progress in harmonizing drug approval requirements under the auspices of a new international body, the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceutical Products (ICH). Vogel (2002) argues that implementation of ICH guidelines has improved both the effectiveness and efficiency of government regulation on pharmaceuticals. Streamlining of bureaucratic processes even among government regulatory agencies that have dealings with the pharmaceutical industry regulation within the country is equally essential to lessen the burden of regulation and Inspections on the manufacturers. Many countries and regions are gradually coming together to develop technical guidelines on pharmaceutical regulations that are uniform among the participating authorities in order to enhance product registration and certification. 'Regulatory Convergence' is the new drive in the pharmaceutical regulation among national regulatory agencies. In a paper presentation on "Current State and Future Directions for Harmonization" Regulatory Convergence ''represents a process whereby the regulatory requirements across countries or regions become more similar or 'aligned' over time as a result of the gradual adoption of internationally recognized technical guidance documents, standards and scientific principles, common or similar practices and procedures, or adoption of regulatory mechanisms that might be specific to a local legal context but that align with shared principles to achieve a common public health goal" (Mukanga D, 2019).

Nigeria is currently ranked 131 among 190 countries in the ease of doing business, according to the latest 2020 World Bank annual ratings (Doing Business, 2020). The ease of doing business index ranks countries against each other based on how the regulatory environment is conducive to business operation and stronger protection of property rights with economies with a high rank from 1-20 having simpler and more friendly regulations for business. A situation of dual regulation of pharmaceutical manufacturing in Nigeria, with the attendant requirements by each of the government agency to be met by the manufacturers, affects the “ease of doing business “ hence streamlining the requirements is a ncessity.

METHODS

The setting for this study is Edo State, a south-south region of Nigeria. The analysis of this paper was based on document review of the two agencies’ acts, the inspection tools used by each agency, corrective and preventive action plans (CAPA) issued within an inspection cycle as well as literature review of best practices in selected countries across the world.

A review of the acts setting up each agency was carried out to establish the responsibility and authority each has over pharmaceutical manufacturers in Nigeria. Enabling parliamentary acts of the two agencies, and core mandates are presented in Table 2.

The law setting up PCN was formerly known as “Pharmacists Council of Nigeria, Decree 91 of 1992.” Created by the repeal of the “Pharmacists Acts of 1964” and this is now known as PCN Acts P17, LFN, 2004.” The mandate of PCN includes:

a) training of pharmacists and pharmacy technicians,
b) registration of pharmacists and pharmacy technicians and keeping of their register,
c) preparing codes of conduct for the profession and reviewing same from time to time, and powers to discipline erring practitioners.
d) regulation and control of the practice of the pharmacy profession which includes registration and licensing of all premises including manufacturing facilities where pharmacists practice their profession (PCN Act P17, LFN,2004).

This study revealed that Pharmacists Council of Nigeria is a product of several reviews and repeals of old pharmacy and drug laws in Nigeria. Such laws include the Poison and Pharmacy Ordinance of 1923, Poison and Pharmacy Ordinance of 1927, Poison and Pharmacy Ordinance of 1936, the Poison and Pharmacy Act 152 of 1958, the Pharmacists Act 26 of 1964. The primary objectives of the Pharmacists Act 26 of 1964 were regulation of the production, sale, supply of drugs. The Act also made room for different levels of control for the various classes of medicines, drugs and poisons. By this act PCN inherited all functions of the former Pharmacy Acts. In discharging of its statutory function, PCN has made regulations such as Regulation No 81 of 2005 concerning registration of pharmaceutical premises to register and certify all premises (including pharmaceutical manufacturing) where pharmaceutical activities take place in Nigeria. (PCN Regulation No. 81, 2005).

As the reforms of the Nigerian pharmacy and drug laws were being carried out, the Federal Ministry of Health from which PCN was created, retained some aspects of the regulatory authorities over pharmaceuticals in its Foods and Drugs Administration and Control Department (FDAC). The FDAC was deemed ineffective and lacked the capacity to ensure quality and safety of pharmaceuticals by stakeholders owing to the growing presence of counterfeit medicines in the country, partially owing to lack of laws concerning fake and counterfeit medicines.

The formation of NAFDAC was inspired by a 1988 World Health Assembly resolution requesting member countries’ help in combating the global health threat posed by counterfeit pharmaceuticals. In 1993 a legislation known as Decree No. 15 of 1993 came into effect and NAFDAC was formed as a parastatal under the Federal Ministry of Health, taking over some of the functions of the Food and Drugs Administration and Control Department (FDAC). NAFDAC acts mandate it to carry out the following functions:

a) regulation of the production, advertisement, import and export, and use or sale of all drugs and foods in Nigeria;
b) carry out among other things, appropriate laboratory assessments and investigation to ensure compliance with standard specifications of all drugs, foods, medical devices, chemicals and table water;
c) inspection of imported foods and drugs for quality assurance;
d) certification of the production sites and of the regulated products;
e) compilation of standards for all manufactured or imported foods, drugs and chemicals;
f) registration of foods and drugs;
g) issuance of quality certificates for foods and drugs.

A comparative analysis of the functions of the agencies was carried as out as shown in Table 3 and Table 4 to examine similarities and possible duplication of functions. Areas of overlap include GMP inspections, collection of fees, authority to penalize and authority to seal premises and registration requirements.

There are seven pharmaceutical manufacturing companies in the study setting, out of which only five were active at the time of the study. Samples of CAPA reports issued by the two agencies to the 5 functional manufacturing facilities were selected for study based on the accessibility of these facilities to the researchers to examine the contents for similarities.

A review of corrective and preventive action documents issued within an inspection cycle by each regulatory agency to these five companies revealed mostly the same pattern and similar CAPA were issued differently by the agencies to the companies.

A review of the agencies' inspection tools was carried out and content indicated the WHO GMP inspection template and guidelines were relied upon and utilized by the regulatory agencies for their audits.

The country presently has no company that manufactures Active Pharmaceutical Ingredients, (APIs), hence the inspections are for Finished Pharmaceutical Products, (FPP). The review showed that both agencies' inspection reports cover concerns on premises layout, equipment, and procedures. In addition, PCN during inspection deep dived into personnel matters while NAFDAC deep dived into the product issues. This is because PCN has the sole responsibility of to license Pharmacists at the premises and NAFDAC has the sole responsibility of registering the products. However, both agencies report generally on the other areas of GMP during their outings.

A search was conducted for structure of pharmaceutical regulatory frameworks using Google Scholar and four countries one each from west, east, south and north Africa as samples while one country each from the other continents of the world were selected and reviewed.

Reports from a 2011 global project by the United Nations Industrial Development Organizations (UNIDO), on the Pharmaceutical sector profile in African Countries, showed the pharmaceutical regulatory frameworks available in those countries. Information on the websites of developed countries' regulatory authorities like the US FDA, EMA, etc. revealed the regulatory frameworks in the pharmaceutical sector. Most of these searches revealed a single regulatory authority in place for pharmaceutical manufacturing as compared to the dual structure in Nigeria.

Table 2. Mandates of Pharmaceutical Regulatory Agencies in Nigeria

Regulatory Agency	Pharmacists Council of Nigeria	National Agency for Food and Drug Administration and Control
Enabling Act of Parliament	Act Cap P17 LFN 2004	Act Cap N1 LFN 2004
Core Mandate	Regulation of Pharmacy and Pharmacy Practice.	Regulation of drugs, Foods bottled water and Chemicals.

Table 3. Dual Regulatory Authority Over Pharmaceutical Manufacturing Premises in Nigeria

Description of Item	**PCN**	**NAFDAC**
Authority to register drugs	No	Yes
Authority to certify personnel (pharmacists)	Yes	No
Authority to inspect site for approval	Yes	Yes
Collection of fees for services (administrative charges)	Yes -inspection fees -premises license fees -personnel licensing fees	Yes -product license fees
Authority to seal premises	Yes	Yes
Authority to penalize	Yes	Yes
Authority to register premises	Yes	No
Authority to inspect facility for certification	Yes	Yes

Table 4. Registration Requirements for Intending Pharmaceutical Manufacturer in Nigeria

Description of requirements	**PCN**	**NAFDAC**
Submission of list of products to be manufactured	Yes	Yes
List of equipment for production and quality control departments	Yes	Yes
List and sources of suppliers of raw and packaging materials	Yes	Yes
Standard operating procedures (SOP)	Yes	Yes
Design of factory layout and production flow chart	Yes	Yes
Company’s organogram/reporting structure	Yes	Yes

Requirement that the company must have at least one pharmacist on its Board of Directors and a Superintendent Pharmacist to register the premises	Yes	Yes
Water source and treatment facilities	Yes	Yes
Water analysis report (raw and treated water)	Yes	Yes
List of qualified staff showing qualifications and duty	Yes	Yes

RESULTS AND DISCUSSION

The purpose of this report was to examine the Acts setting up the Pharmacists Council of Nigeria (PCN) and the National Agency for Food and Drugs Administration and Control (NAFDAC) as well as the GMP inspection tools used by both agencies with a view to finding areas of overlap that usually result in duplication of functions. Practices of regulatory inspection and approval in the two agencies were also reviewed with the intention of identifying ways to lessen the burden of inspection and avoid delays in product release.

Regulatory inspection of pharmaceutical manufacturing facilities is a vital element of good manufacturing practice compliance. Harmonization of inspections and supervision by regulatory authorities to avoid different interpretations by manufacturers is equally important in ensuring standards of quality of pharmaceutical products. Recent studies in Pakistan identified coexistence of pharmaceutical manufacturing facilities operating under different GMP standards and interpretations as being a failure of the national drug regulatory authority not carrying out effective inspection and supervision. Recent studies in Pakistan described the coexistence of pharmaceutical manufacturing facilities operating under different GMP standards and interpretations. The differences resulted from a failure of the national drug regulatory authority to carry out effective inspection and supervision. The Pakistan regulatory authority had failed to achieve a state of quality and compliance. In Pakistan, the need for global harmonization of quality standards and regulatory supervision was recognized (Tauqeer et al. 2019).

When inspection and directives are carried out by a single government regulatory agency, there is less regulatory burden for manufacturing companies and greater access to quality products as compared to two government regulatory agencies, as exists in Nigeria.

In a study on impact of regulatory requirements on medicine registration in Africa, it was reported that GMP inspection by regulatory agencies was a barrier to the registration and supply of medicines. High fees of GMP inspections and other regulatory activities contributed to the barrier. (Narsai et al. 2012).

Reducing the burden of inspections on regulators is also important due to the growing number of facilities to be inspected and the limited resources of the regulatory agencies. In the United States, the risk-based approach initiative on inspections by the FDA is worth mention. In the risk-based approach, an FDA's certified agent carries out the inspection on behalf of the FDA on selected 'low priority' inspections. This practice frees time and space for the FDA so as to concentrate on 'high priority' facilities and enforcement activities to ensure timely registration and release of products to the market. (National Academies Press (US), 2010).

The study considered compliance directives issued by PCN and NAFDAC between 2012 and 2018 to two manufacturing firms in Edo State, Nigeria. These are herein referred to as Pharma A Nig. Ltd and Pharma B Nig. Ltd. Pharma A manufactures external preparations and Pharma B manufactures oral liquid preparations.

During this period, NAFDAC visited Pharma A five times for inspections and visited Pharma B Nig Ltd four times. Similarly, within the same period, PCN made 3 visits each to Pharma A and B as presented in Tables 5 and 6.

Of the 14 items of CAPA, both agencies gave Pharma A similar directives on 12 items, representing (86%) (Table 5). Both agencies gave Pharma B 17 similar CAPAs out of the 22 items, representing

(77%) (Table 6). The similarity of directives likely occurred because the same GMP inspections template was used on the same facility. Collaboration between the agencies could have reduced the number of inspection visits by each agency, reduced the costs to the manufacturer and reduced the use of human and material resources by the regulatory authorities. The latter outcome would be desirable since both agencies are financed by the federal government.

Table 5: Summary of Nature of CAPA issued by the Regulatory Agencies between 2012 and 2018 to Pharma A Nig Ltd.

Nature of CAPA	NAFDAC from the 5 inspections visits within the period under review	PCN from the 3 inspections visits within the period under review
-lab analysis related issues	Yes	Yes
-SOP related issues in the QC lab	Yes	Yes
-medical records of personnel and related issues	Yes	Yes
-inadequacy of utensils in production room (stainless-steel containers etc)	Yes	Yes
-environmental sanitation of surrounding/ demand for provision of environmental impact analysis report	Yes	Yes
-issues related to flooring and window fittings of production room	Yes	Yes
-UV air sterilizer related issues	Yes	Yes
-production room windows related issues	Yes	Yes
-cloak room related issues	Yes	Yes
-raw material store related issues	Yes	Yes
-inadequacy in Microbiology lab instruments	Yes	Yes
-validation master plan related issues	Yes	Yes
-in-process related issues (batch manufacturing records, etc)	Yes	no
-personnel training issues	No	Yes

Table 6: Summary of CAPA issued by the Regulatory Agencies between 2012 and 2018 to Pharma B Nig Ltd. (company manufactures oral liquid preparations)

Nature of CAPA	NAFDAC from the 4 inspections visits within the period under review	PCN from the 3 inspections visits within the period under review
-SOP related issues	Yes	Yes
-water treatment related issues	Yes	Yes
-finished product analysis related issues	Yes	No
-lack of specific in-process test for determining total clearance of jelly from filling machine	Yes	No
-monitoring devices on equipment and related issues	Yes	No
- storage of raw material related issues (provision of pellets etc.)	Yes	Yes
-water treatment related issues	Yes	Yes
-ceiling in production room related issues	Yes	Yes
-inadequacy of equipment in microbiology lab	Yes	Yes
-inadequacy of reagents in the lab and related issues	Yes	Yes
-hygiene related issues (hand washing facilities etc.)	Yes	Yes
-monitoring devices (temp & humidity) in stores and related issues	Yes	Yes
-equipment for in-process operations	Yes	Yes
-inadequacy of flooring of production room and related issues	Yes	Yes
-extractor fans related issues in production room	Yes	Yes

-validation master plan issues	Yes	Yes
-raw material storage related issues	Yes	Yes
-receiving bay related issues	Yes	Yes
-documentation related issues	Yes	Yes
-issues related to inadequacy of equipment and materials in the microbiology lab	Yes	No
-company organogram related issues	Yes	Yes
-quality manuals related issues	Yes	No

CONCLUSION

This study demonstrated that the two Nigerian pharmaceutical regulatory agencies, PCN and NAFCAC, have overlapping regulatory functions. Their duplicated efforts cause excessive regulatory burden on the Nigerian pharmaceutical industry, potentially limiting the availability of quality drug products. The WHO guidelines for inspection of pharmaceutical manufacturing facilities is a template for all to follow. These guidelines stem from GMP, which is the same irrespective of which agency is involved. It is recommended that both agencies collaborate to lessen the burden of frequent visits to the manufacturers for the purpose of inspection.

The study identified that most of the corrective and preventive actions (CAPA) issued by both Nigerian agencies to the same manufacturing facilities were similar. However, the manufacturer has to prepare separately for each agency's visit, thereby increasing their burden. It is recommended that PCN and NAFDAC collaborate to address issues of inspection by adhering to globally accepted Good Manufacturing Practice templates, such that inspection done by an agency can be used as a template by the other regulatory agency. Clear inspection boundaries will reduce the burdens of inspections on both the regulators and the manufacturers. Clear boundaries will also reduce cost and improve effectiveness of the regulatory activities by ensuring better use of resources through a memorandum of understanding or collaboration between the PCN and NAFDAC as it relates to inspections of these facilities. The challenge of the duplication of function is that of policy, hence government and legislative intervention may take time. However, a possible joint inspection by the two agencies can help in reducing the different misinterpretation of GMP aspects of inspection by the agencies and the burden on manufacturers and the regulators themselves.

RECOMMENDATIONS FOR NEXT STEPS

The findings of this study are from a single state in Nigeria. It is recommended that a comprehensive study of activities of the two regulatory agencies be conducted across the entire country to get the true perspective of the burdens placed on manufacturers as a result of dual regulations, especially on inspection.

It is also recommended that a policy be created to clearly define boundaries of the two regulatory agencies. The Pharmaceutical Society of Nigeria (PSN), which is the umbrella body of pharmacists in Nigeria, has a significant influence on pharmacy regulation in Nigeria. Seeking opinion and cooperation of the PSN may help to address the harmonization recommended in this study.**REFERENCES**

Altenstetter, C. (2012) Medical device regulation in the European Union, Japan and the United States. Commonalities, differences and challenges. *Innovation: The European Journal of Social Science Research,* 25**,** 362-388.

Drug Administration. Washington (DC): National Academies Press (US); 2010. 8, Enhancing the Efficiency of Inspections. Available from: https://www.ncbi.nlm.nih.gov/books/NBK220393/ (Accessed January 3, 2020).

Pharmacists Council of Nigeria, Act 91 of 1992 (Now Act P.17, LFN 2004), Law of Federal Republic of Nigeria, 2004.

Government of Nigeria. Pharmacists Council of Nigeria, Registration of Pharmaceutical Premises, Regulation No.81, 2005

Inspection. (2010) In Business Dictionary.com. Retrieved January 01, 2020, (Altenstetter 2012)from http://www.businessdictionary.com/definition/inspection.html

International Society for Pharmaceutical Engineering (ISPE), (n.d.). Good manufacturing practice (GMP) Resources retrieved January 22nd,2020 from https://ispe.org/initiatives/regulatory-resources/gmp#

Mukanga, D. (2019, September). Current State and Future Directions for Harmonization. Presented at Kilimanjaro Purdue Session, Arusha, Tanzania. Sept. 5, 2019.

Narsai,K.,A.Williams&A.K.Mantel-Teeuwisse (2012). Impact of regulatory requirements on medicine registration in African countries-perceptions and experiences of pharmaceutical companies in South Africa.*Southern med. Reviews*,5,31-37.

National Academies Press (US); 2010. 8, Enhancing the Efficiency of Inspections. Available from: https://www.ncbi.nlm.nih.gov/books/NBK220393/. (Accessed January 3, 2020).

National Agency for Food and Drug Administration and Control (n.d.). Drugs and Related Products Registration Regulations, 2019.

National Agency for Food and Drug Administration and Control Act 2004. c.1.*Available at* https://nlipw.com/research-laws-africa/nafdac-act/. (Accessed on 20th January 2020)

Nigeria National Drug Policy,2005.Available at

National Research Council (US) Committee on the Review of Food and Drug Administration's Role in Ensuring Safe Food; Wallace RB, Oria M, editors.

Pharmacists Council of Nigeria (PCN). History of Pharmacy Regulation in Nigeria. Pharmacists Council of Nigeria, Abuja, Nigeria, 2001.

Pharmacists Council of Nigeria Act ,2004 c.1. Available at https://nlipw.com/pharmacists-council-nigeria-act/ (Accessed 22nd January 2020).

Scott, J. 2009. *GMA Perspective on FDA's Role in Ensuring Safe Food*. Paper presented at Institute of Medicine/National Research Council Committee on Review of the FDA's Role in Ensuring Safe Food Meeting, Washington, DC, March 24, 2009.

Tauqueer,F.,K.Myhr &U.Gopinakan(2019). Institutional barriers and enablers to implementing and complying with international acceptable quality standards in the local pharmaceutical industry of Pakistan:a qualitative study.*Health policy and planning*, 34,440-449.

Vogel, D (2002). The Globalization of Pharmaceutical Regulation. Retrieved from https://onlinelibrary.wiley.com/doi/abs/10.1111/0952-1895.551998055. January 4,2020.

WHO Technical Report Series, No. 986; http://www.who.int/ medicines/publications/pharmprep/en/index.html, accessed on 6th April, 2020.

WHO Website https://www.who.int/medicines/areas/quality_safety/quality_assurance/gmp/en/. Accessed on April 17, 2020.

World Health Organization (2007). *Quality assurance of pharmaceuticals a compendium of guidelines and related materials. Volume 2,Good manufacturing practices and inspections*. World Health Organization.

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.