Chapter 5

Application of ISO 9001 Industrial Standard to Herbal Drug Regulation

Sunday Ameh, Florence Tarfa, Magaji Garba and Karniyus Gamaniel

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/50814

1. Introduction

We noted earlier [1] that 1978 was the turning point in current public perception of traditional medicine (TM) following the famous WHO declaration at Alma-Ata. That declaration ushered in a positive attitude that paved the way for the present global popularity of TM, especially herbal medicine. We noted earlier also [2,3] that whereas herbal remedies are called dietary supplements in the US, thereby shifting emphasis away from their medicinal attributes, the Dietary Supplement Health Education Act of 1994 [4], which occasioned the shift, actually helped to promote herbal medicine in the US, albeit indirectly, through the innovative provision it made for user information [5,6]. A similar situation obtained in Europe, where the net effect of the laws and rules passed in 2004 on herbal remedies had been to promote their production and use [7, 8]. In terms of trade and economics of herbal drugs, the following fact is notable: Although, Asia contributed only US$ 7.3 billion to herbal world trade in 1999 [9], by 2005, a mere 6 years, China's contribution alone rose to US$ 14 billion [10]. This stupendous growth was due to policies and programmes that favoured herbal medicine – the cornerstone of Traditional Chinese Medicine (TCM). Similar situations as in China held sway in Japan, South Korea and the Indian sub-continent, where government policies also favoured herbal medicine. However, in many developing countries like Nigeria, a totally different picture obtained, not because policies were expressly against herbal medicine, but in these countries there had been a lingering absence of proper policies and laws supportive of traditional remedies. Another key fact on the political economy of herbal drugs is that: Although, about 80% of people in developing countries depended on herbs, these countries contributed only 7.2% to herbal drug trade in 1999. By contrast, the developed nations, where people relied less on herbs, contributed 55.2%. Asia, less Japan and

South Korea, contributed 37.6%. Equally interesting is the comparison of Brazil with Nigeria. Both are rich in medicinal plants and have high populations that depend substantially on herbs. But, while herbs contributed an unknown amount to the Nigerian economy in 2007, in Brazil it contributed US$ 160 million. By contrast, Nigeria's entire federal budget for health in 2007 was a mere US$ 800 million [2]. These findings earlier led us [11,12] to conclude that developing countries need strategies that will enhance the regulation of herbal drugs and promote their trade. The present article is an attempt to enunciate one of such strategies. It is particularly of note that the superior performance of Brazil in comparison with Nigeria indicates that with proper policies and strategies, herbs can indeed contribute substantially to any economy.

2. Methodology: Determinative Review of ISO 9001 and the Mandates of Nigeria's and Europe's DRAs

2.1. ISO 9001:2008 industrial standard – A synopsis

ISO 9001:2008 industrial standard or quality management system (QMS) is a document of about 30 pages with 8 clauses, published by and obtainable from the International Organization for Standardization (ISO), Basle, Switzerland, or from any of its national affiliates. The standard is designed to be met by any organization that i) needs to demonstrate its ability to consistently provide product or service that meets both customer and applicable statutory and regulatory requirements (collectively legal requirements); ii) aims to enhance customer satisfaction by effectively and continually improving its QMS; and iii) plans to provide continual assurance of conformity to customer and applicable legal requirements. These aims/ approaches (often called "QMS requirements" or "quality procedures") are generic and intended to be applicable to all organizations regardless of type, size and product provided. Wherever any requirement cannot be applied due to the nature of an organization and its product, such can be considered for exclusion. But wherever exclusions are made, claims of conformity to the standard are not acceptable unless such exclusions are limited to requirements within clause 7 of the standard, and such exclusions do not affect the organization's ability, or responsibility, to provide product that meets customer and applicable legal requirements. ISO 9001:2008 defines the minimum requirements for a well managed organization. In other words, noncompliance to an ISO 9001:2008 requirement puts at risk an organization's ability to consistently and efficiently satisfy the expectations of its customers/ stakeholders.

2.2. The six QMS requirements or "The Six Quality Procedures"

These procedures or requirements, as one may choose to call them, actually refer to subclause 4.1 (General requirements) under clause 4 (Quality Management System) of ISO 9001:2008. The sub-clause prescribes that organizations shall establish, document, implement, and maintain a QMS, and continually improve its effectiveness. To do so means that the organization shall operate its QMS with a view to carrying out (or meeting) the following six procedures (or requirements): determine the processes needed for the QMS, and their

http://dx.doi.org/10.5772/50814

application throughout the organization; determine the sequence of the processes and their interactions; determine the criteria and methods for operating and controlling the processes; determine and ensure the availability needed resources and supporting information; check, measure and analyze the processes, where applicable; and implement actions to achieve planned results and continual improvement of the processes.

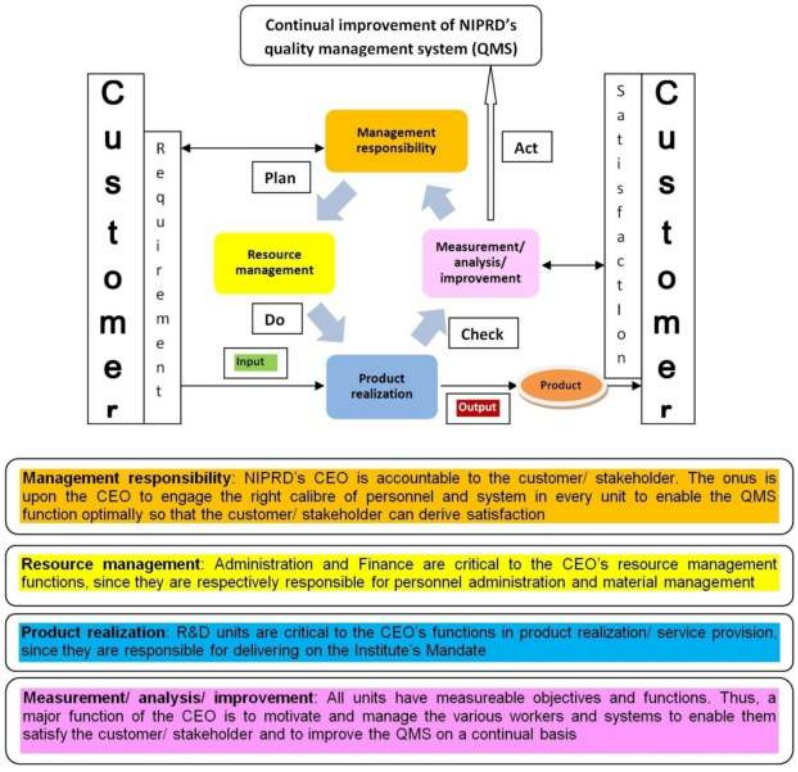

Figure 1. NIPRD's core business in the context of Plan-Do-Check-Act process-based QMS.[1]

The organization shall manage the processes above in accordance with ISO 9001:2008 requirements. It shall also define the type and extent of control to be applied to any outsourced process that can affect product conformity to requirements. ISO 9001:2008 specifically notes as follows:

1 Management responsibility corresponds to clause 5 of ISO 9001; while Resource management, Product realization and Measurement/ analysis/ improvement correspond to clauses 6, 7 and 8 respectively.

1. Processes needed for the QMS include the processes for management activities (clause 5), provision of resources (clause 6), product realization (clause 7), and measurement, analysis, and improvement (clause 8).
2. An outsourced process is a process the organization needs for its QMS, and which the organization chooses to have performed by an external party.
3. Ensuring control over outsourced processes does not absolve the organization of the responsibility to conform to customer and legal requirements.

The type and extent of control applied to an outsourced process can be influenced by factors such as: the potential impact of the outsourced process on the organization's capability to provide product that conforms to requirements; the degree to which the control over the process is shared; and the capability of the organization in achieving the necessary control via the application of sub-clause 7.4 (Purchasing). Philosophically, ISO 9001:2008 is formulated on the basis of management by objectives (MBO) and draws upon eight quality management principles. Ideally therefore, quality assurance covers activities in research, development, production and documentation. It embraces the rule: "do it right the first time". It involves regulating the quality of raw materials, the state of production line and works-in-progress, the product and related management processes. One of the most widely used paradigms for quality assurance management (QAM) is the “Shewhart cycle”, also called “PDCA approach”, meaning, “Plan-Do-Check-Act” [13,14]. The foregoing is illustrated in Figure 1 using NIPRD QMS processes as an example.

2.3. The eight quality management principles that underlie ISO 9001:2008

Like other ISO standards (Example: ISO 9004 - *Managing for Sustained Success*), ISO 9001:2008 is based on 8 quality management principles that are aligned with the philosophy and objectives of most quality award programmes in the world’s most industrialized nations. The 8 principles are associated with the following themes:

1. Customer focus.
2. Leadership.
3. Involvement of people.
4. Process approach to management.
5. System approach to management.
6. Continual improvement.
7. Factual approach to decision making.
8. Mutually beneficial supplier relationships.

http://dx.doi.org/10.5772/50814

2.4. Key terminologies of ISO 9001:2008

2.4.1. Process approach to management

A process is an activity or operation that receives inputs and converts them to outputs. Practically all activities or operations involved in generating a product or providing a service are processes. For an organization to function, it must define and manage several inter-linked processes. Most often, the output of one process becomes the input into the next process. The systematic identification and control of the various processes employed within an organization, and the interactions between such processes, is termed "process approach" to management. Thus process approach to management is a way of obtaining a desired result, by controlling activities and related resources as a process. Process approach is a key element of all ISO 9000 standards, including ISO 9001:2008.

2.4.2. System approach to management

System approach to management is based on the premise that the efficiency and effectiveness with which an organization achieves its quality objectives are contributed and enhanced by identifying, understanding and managing all the interrelated processes within the organization as a system

2.4.3. Quality policy

Quality policy is a formal statement from the management of an organization that is linked to the nature of its business and its plans to meet the needs of its customers/ stakeholders. The policy is designed to be understood and followed at all levels and by all staff.

2.4.4. Quality objective

Quality objective is the factual or tangible basis upon which quality policy and plans for implementing the quality programmes of an organization are built. Quality objective should be SMART (ie: specific, measurable, achievable, realistic and time-bound). Each staff of the organization is expected to work towards measurable objectives.

2.4.5. Decision

Decision simply means the selection of one or more options from a multitude of options in tackling a given organizational task. As far as the QMS is concerned, an organization should make SMART decisions based on recorded data. An example of a SMART decision is: The QMS must be audited and evaluated regularly for conformance and effectiveness, so as to assure quality and continual improvement.

2.4.6. Traceability

Traceability is concerned with and refers to the fact that typically, recorded data are meant to show how and where raw materials and products were processed, in order to allow products and problems to be traced to their sources.

2.4.7. Product realization

Product realization refers to the scenario in which, when developing a new product, an organization plans the stages of development, with appropriate testing at each stage. The organization tests and documents whether the product meets design requirements, legal requirements, and user or customer needs.

2.4.8. Quality plan

Quality plan refers to a document specifying the QMS processes (including the product realization processes), and the resources to be applied to a specific product or project.

2.4.9. Monitoring and measurement

Monitoring and measurement refer to the scenario in which an organization must regularly review its performance through meetings and internal audits, and determine whether the QMS is working and what improvements can be made. The organization must have a documented procedure for internal audits and a procedure for dealing with past problems and potential problems. It must keep records of these activities and the resulting decisions, and monitor their effectiveness. It must have documented procedures for dealing with actual and potential nonconformances (problems involving suppliers, customers, or internal problems).

2.4.10. Continual improvement

Continual Improvement refers to the scenario in which an organization 1) makes sure no customer uses a bad product, 2) determines what to do with a bad product, 3) deals with the root cause of problems, and 4) keeps records to use as a tool to improve the QMS.

2.4.11. Customer requirements

Customer requirements refer to the attributes that the buyer of a product (or user of a service) wants. The core business of an organization is to determine customer requirements and to meet them, in accordance with sub-clause 5.2 (Customer focus).

2.4.12. Drug Regulatory Agencies (DRAs)

Drug regulatory agencies (DRAs) are organizations set up by the State on behalf of the general public with a Mandate to regulate drugs and related products and services. The Mandate of some DRAs may include production and distribution of certain goods like vaccines and orphan drugs. Either the State or the general public can be regarded as customer, stakeholder or shareholder. DRAs like all other organizations must have a system for communi-

http://dx.doi.org/10.5772/50814

cating with customers or stakeholders about product information, inquiries, contracts, orders, feedback, and complaints. All DRAs are "service providers" but some produce and even distribute certain specific items, as mentioned above. Nigeria's National Agency for Food and Drug Administration and Control (NAFDAC) is a national DRA, while the European Medicines Evaluation Agency is a regional DRA.

2.4.13. Mandate

Mandate is a piece of legislation or instruction from a constituted authority to another constituted authority or body to carry out a named task. DRAs are mandated by the State to regulate drugs and health related products.

2.5. The new industrial revolution and the aim of this chapter

It is well established that the high state of development in the chemical/ pharmaceutical industrial sector in the US, Japan, South Korea, Britain, Germany and other European countries owes much to the powerful synergy between regulatory legislations, industrial standards and a focused political will. It is also manifest that the rapid, all-round industrial revolution in China in the past decade or so owes much to China's embrace of ISO standards, especially ISO 9001, as shown in Table 1 after a recent [15].

Country	Ranking	No. certificates	Pertinent remark
China	1	257,076	Relies mostly on ISO standard.
Italy	2	130,066	Relies mostly on ISO standard
Japan	3	68,484	Relies only partly on ISO standard
Spain	4	59,576	Relies substantially on ISO standard
Russia	5	53,152	Relies substantially on ISO standard
Germany	6	47,156	Relies only partly on ISO standard
UK	7	41,193	Relies only partly on ISO standard
India	8	37,493	Relies substantially on ISO standard
South Korea	9	28,935	Relies substantially on ISO standard
US	10	23,400	Relies only partly on ISO standard

*Source ISO Survey 2009 [15]. Most countries have their own national standards in addition to ISO standards. For example the UK is well known for its industrial standards pre-sufixed by BSI (British Standards Institution).

Table 1. The top 10 countries in ISO certification in 2009.

It must be stated that countries like Japan, Germany, Britain and US use their own national standards in addition to those of ISO. Based on the foregoing, we state that the specific aim of this article is: To examine the QMS requirements of ISO 9001:2008 and the requirements

for regulating herbal drugs in Nigeria (a developing economy) and Europe (a developed economy), with a view to devising a framework that will better regulate herbal drugs and facilitate their trade worldwide. Such a framework will greatly benefit developing countries like Nigeria that are yet to benefit optimally from their comparative advantage in the abundance of spices, herbs and medicinal plants. In addition, marketers and users of herbs in consumer nations like the US, Canada, Germany, UK and France, where consumption now runs in to billions of US dollars, will also profit greatly from an improved and regularized world trade in herbs.

3. Results & discussion: A Framework for Efficient Herbal Drug Regulation (HDR)

3.1. Justification for establishing national or regional DRAs

Most or all countries have a national or regional agency that regulates the production, distribution and use of drug products. The process of regulation commences with the registration of the producer, the product, the distributor and in some cases the user. In some countries drugs, foods and dietary supplements are regulated by the same body (eg: Nigeria's NAFDAC and US-FDA). The EU's EMEA however regulates only drug products. States or regions need to have DRAs in order to ensure order in the production, distribution and use of drugs. Without DRAs utter chaos and pandemonium will result in production (eg: manufacturers will do as they please without a uniform control), distribution (distributors and suppliers will do as they choose without a uniform order) and use (prescribers and users will do as they think without a uniform regime), which would allow incidences of counterfeit and expired drugs in drug distribution chain, drug abuse and emergence of drug resistant disorders, especially infective conditions like malaria and TB.

3.2. Comparative analysis of Nigeria's and EU's requirements for herbal drug regulation

A careful scrutiny of the requirements for registering and regulating herbal drugs in Europe and in Nigeria reveals their basic similarity, as shown in Table 2.

European Union (EU) – regulated by EMEA		Nigeria – regulated by NAFDAC	
Type of data	**Details of data required**	**Regulatory aspect**	**Requirement**
Product information: Summary of product characteristics	These include: name, strength, dosage form, list of excipients, shelf life, posology, indications, contraindications, and special precautions. These are used as basis for inserts or advertisement, which must undergo a process called "readability".	Legal status of applicant - manufacturer or marketer	Applicant must be certified by the Corporate Affairs Commission as a business. A marketer must show evidence of Power of Attorney.

http://dx.doi.org/10.5772/50814

European Union (EU) – regulated by EMEA		Nigeria – regulated by NAFDAC	
Type of data	**Details of data required**	**Regulatory aspect**	**Requirement**
Quality control data: Refer to GMP requirements for production.	These include: production must be in a GMP compliant, product must be produced with validated formula and method, there must be a product specification, stability studies must be carried out in the container proposed for marketing for purposes storage/ shelf-life, and dossiers must be provided for starting materials and finished product.	Analytical status of the product for registration.	The product must have: certificate of analysis, dossier containing data on ingredients, method of analysis, stability, dosage and safety precautions.
Safety data requirements	The data may be assembled from: animal or human studies, review of potential drug-drug interactions, side effects and contraindications. Others include: recognized monographs, data special groups - children, the elderly and mothers.	Pre-registration inspection of premises.	Manufacturing, storage and distribution premises must be GXP compliant. Marketers must provide convincing evidence of GXP
Traditional use evidence	Evidence that the product has been in use as medicine for 30 years or more (the last 15 must be in the EU. Notably, there is no requirement to prove efficacy (De Smet, 2005).	Post marketing surveillance plan/ report	Applicant may be required to provide a plan for reporting on the use of the product and of any adverse reactions.
-	-	Others, such as fees and waivers.	Fees are required at several stages of the registration but waivers are not expressly stated, thereby negating the concept and need for transparency (see Table 3 for extra requirements).

*The Table was drawn based on data gathered from references including Goldman [5]; De Smet [7, 8]; Ann Godsell Regulatory [16]; and various NAFDAC leaflets, including Akunyili [17]. Note that the requirements for registration in Nigeria are not necessarily less tasking, but their lack of explicitness can be a booby trap and a leeway for non-transparency. The necessity for explicitness and transparency is very important because some years ago the Director General of China's drug regulatory agency was sentenced to death for alleged corrupt practice [18]. In 2000 the entire Management of NAFDAC was sacked in similar grey circumstances.

Table 2. Requirements for herbal registration compared between EU and Nigeria.

But, while the EMEA approach is technically more explicit, though not necessarily more exerting than NAFDAC's, the latter is administratively much more cumbersome, and therefore more liable to inefficiency and abuse. Table 3 shows the extra bureaucratic demands of NAFDAC. We stated earlier that, although, 80% of people in developing countries like Nigeria depended on herbs, these countries contributed only 7.2% to herbal drug trade in 1999. By contrast, the developed nations, where people relied less on herbs, contributed 55.2%. This scenario is explained by the fact herbal drugs are better regulated in developed regions like the China, India, Japan and South East Asia, the EU and North America [2].

3.3. Justification for selecting ISO 9001:2008 for this study

Although most of the OECD countries and other highly industrialized economies, where herbal drugs are well regulated, have their own national standards, all do embrace ISO standards, especially ISO 9001:2008. For example, the British Standards Institution (BSI) is well known and widely adopted in many other countries worldwide, and although international in application, such national standards do not bear the tag "international". By contrast, the ISO family of standards bear the tag "international". ISO 9001:2008 is an international standard designed to address systemic change (ie: a change that affects an organization as a whole). The global popularity of ISO 9001:2000 - the predecessor of ISO 9001:2008, is attributable to the following factors: a) major purchasers require their suppliers to hold ISO 9001 certification [15, 19]; b) studies indicate significant financial benefits for organizations certified to ISO 9001 [19,20]; and c) similar superior operational performance of ISO certified firms has been severally confirmed [21-24]. As just noted, ISO 9001:2008 is an update of ISO 9001:2000, and we have selected it for this study by reason of its popularity and versatility, and because it is a process-based QMS that addresses systemic change affecting whole organizations like a national or regional drug DRA, like Nigeria's National Agency for Food and drug Administration and Control (NAFDAC), the US Food and Drug Administration (US-FDA) and the European Medicines Evaluation Agency (EMEA).

S/No	Extra requirement	Remark
1	Five (5) copies of the product dossier.	Probably unreasonable
2	Three (3) packs of the products samples.	Probably reasonable
3	Notarized original copy of the duly executed Power of Attorney from the product manufacturer.	Clearly unreasonable for all categories of applicants
4	Certificate of Manufacture issued by the competent health or regulatory authority in country of origin and authenticated by the Nigerian Mission in that country. Where there is no Nigerian mission, The British High Commission or an ECOWAS country Mission will authenticate.	Probably unreasonable for all categories of applicants
5	If contract-manufactured, Contract Manufacturing Agreement, properly executed and notarized by a Notary Public in the country of manufacture.	Clearly unreasonable for all categories of applicants
6	Current World Health Organization Good Manufacturing Practice Certificate for the manufacturer, authenticated by the Nigerian Mission.	Clearly unreasonable for all categories of applicants
7	Certificate of Pharmaceutical Products (COOP) duly issued and authenticated.	Clearly unreasonable for all categories of applicants
8	Current Superintendent Pharmacists license to practice issued by the Pharmacists Council of Nigeria (PCN).	Only probably reasonable

http://dx.doi.org/10.5772/50814

S/No	Extra requirement	Remark
9	Premises Registration License from PCN	Only probably reasonable
10	Certificate of Registration of brand name with trademark registry in the Ministry of Commerce here in Nigeria; Letter of invitation from manufacturer to inspect factory abroad, stating full name and location of plant.	Probably unreasonable for all categories of applicants
11	The applicable fee payable only if documents are confirmed to be satisfactory	Likely to be abused if the amount is high. The fee should be a token amount paid by all applicants
12	Nutraceuticals, medical devices and other regulated drug products have similar requirements, with minor variations. Specific details can be obtained from NAFDAC.	A sketch of the minor variations should be provided in print no matter how brief. Any information provided by NAFDAC should be printable for sake of transparency

*The information on NAFDAC were drawn from leaflets and NAFDAC's website (2010): www.nafdacnigeria.org/ The remarks are informed by current affairs and public perception of NAFDAC's role and activities including the wholesale reorganization of its Management in 2000.

Table 3. NAFDAC's extra requirements for registering herbal medicines.

3.4. A systematic review of the eight clauses of ISO 9001:2008 in relation to DRAs

3.4.1. A synopsis of the Mandate of DRAs and the eight clauses of ISO 9001:2008

ISO 9001:2008 is the most widely used QMS standard, with over a million certificates issued worldwide. Alas, it was revealed at the SON-NIPRD course in 2011, that only two public institutions in Nigeria have ISO 9001 certification! Yet, as stated earlier, ISO 9001:2008 defines the minimum requirements for a well managed organization. The standard is published by the International Organization for Standardization (ISO), Basle, Switzerland. National accreditation bodies like the Standards Organization of Nigeria (SON) provide accreditation to registrars who issue the ISO 9001 certificates to those they audit. ISO 9001:2008 is set out in eight clauses designated clauses 1 to 8. The structure and salient points/ directing principles of the clauses are tabulated below. A copy of ISO 9001:2008 is a prerequisite for this study. Similarly required, is a grasp of the requirements for registering and regulation herbal drugs in a developed economy like Europe; and in a developing country like Nigeria, as depicted in Table 2. It is well known that herbal drugs are better regulated in the developed than in developing countries. Table 3 suggests that undue bureaucracy or needlessly cumbersome requirements can hinder efficient regulation. Tables 4-13 show the structure and salient points/ directing principles of the 8 clauses.

Clause	Title and subtitles, with remarks	Salient points/ directing principles/ application to DRAs
1	**1. Scope** **1.1 General** **1.2 Application**	ISO 9001:2008 can be used to establish, and to update a DRA's QMS. A DRA, like other parastatals or private organizations must consider its unique operational environment and the dynamics and risks associated therewith.
2	**2. Normative references** (eg: ISO 9000:2005 is devoted to *QMS Fundamentals and Vocabulary*; and ISO 9004:2009 is devoted to *Managing for Sustained Success*)	A normative reference implies, unless otherwise stated, that the most recent versions of the separate documents should be referenced. DRAs would benefit immensely from such key references and compendia such as the *International Pharmacopoeia* and others like the *BP* and *USP*, and the WHO manual on *Quality Control Methods for Medicinal Plant Materials*.
3	**3. Terms and definitions** (see section 2.4 of this article on "Key terminologies of ISO 9001:2008)	The term "product" may also mean "service". "Legal requirements" means "statutory and regulatory requirements". Most DRAs are service providers only, while others may produce and distribute certain specialized health products.

*The Table is to be studied side by side with the contents of ISO 9001:2008 and Table 2, which is on regulatory requirements of DRAs.

Table 4. Clauses 1-3 of ISO 9001:2008 in relation to DRAs.

Clause	Title and subtitles, with remarks	Salient points/ directing principles/ application to DRA
4	**4. Quality Management System (QMS)** **4.1 General requirements** **4.2 Documentation requirements:** **4.2.1 General** – QMS documents must include: quality policy, quality objective, quality manual, documented procedures/ records specified by ISO 9001:2008, and documents/ records determined by the organization to be relevant for effective planning, operation and control of the QMS. **4.2.2 Quality manual** – this should include the scope of the QMS, SOPs and a description of the QMS processes. **4.2.3 Control of documents** - the documents required by the QMS must be established and controlled. This means that SOPs are to be established to define the controls needed. **4.2.4 Control of records** – records are a special type of documents and must be established and controlled. Here too, SOPs are to be established to define the controls needed. **Note:**1) A document is a piece of written, printed, or electronic matter that provides information or evidence. It may or may exist	Clause 4.1 implies that the DRA must identify, manage and document the processes that make up its QMS – ie: the DRA must address the so called "Six Quality Procedures" and generate relevant documents, including: 1) quality manual, 2) quality policy, 3) quality objective, 4) process flowchart, and 5) work instructions. The DRA can achieve this by using a management strategy called "process approach", which means that it must manage: 1) the processes that make up its organization, 2) the interaction between these processes, and 3) the inputs and outputs that glue these processes together. The quality manual should: 1) describe how the QMS processes interact; 2) define the scope of the QMS (it should explain any reductions in the scope of the QMS and justify all exclusions/ reductions); and 3) document all procedures in the QMS or refer to them. It is most crucial that the DRA prepares, establishes and maintains a quality manual. The DRA must establish SOPs to define the controls needed: 1) to approve, review, update and re-approve documents prior to use; 2) to ensure that changes, current status, relevant versions of documents are identified; and 3) to prevent the unintended use of obsolete documents. The DRA must establish records to provide: 1) evidence that operations conform to QMS requirements; and 2) evidence that operations of the QMS are effective. Records must be ensured to be legible, readily identifiable and retrievable.

http://dx.doi.org/10.5772/50814

Clause	Title and subtitles, with remarks	Salient points/ directing principles/ application to DRA
	in a permanent form. 2) A record is a permanent document of something that is kept for evidence or information. It specifically bears the history of events or arrangements, and is preserved in a lasting form.	

*The Table is to be studied side by side with the contents of ISO 9001:2008 and Table 2, which is on regulatory requirements of DRAs.

Table 5. Clause 4 of ISO 9001:2008 in relation to DRAs.

Clause	Title and subtitles, with remarks	Salient points/ directing principles/ application to DRA
5	**5 Management Responsibility** **5.1 Management commitment** **5.2 Customer focus** – the organization must ensure that its purpose/ focus (inclusive of customer/ stakeholder requirements) is understood and determined. **5.3 Quality policy** – this should be: 1) appropriate to the purpose of the organization; 2) focused on meeting requirements and continual improvement; 3) used as a framework for quality objectives; 4) publicized and understood at appropriate levels; and 5) reviewed for continuing suitability . **5.4 Planning** **5.4.1 Quality Objectives** **5.4.2 QMS Planning** **5.5 Responsibility, Authority, and Communication** **5.5.1 Responsibility and Authority** **5.5.2 Management Representative** **5.5.3 Internal Communication** – it is crucial that the organization ensures that appropriate communication processes regarding the effectiveness of the QMS are established and implemented. **5.6 Management Review** **5.6.1 General** **5.6.2 Review Input** – includes audit results, public feedback, process performance, status of preventive/ corrective action, follow-up from previous management review,	The DRA must be committed to developing and implementing a QMS, as well as, a commitment to continually improve the effectiveness of the QMS. The DRA can do this by 1) communicating the importance of meeting "legal and customer requirements"; 2) establishing a quality policy and quality objectives; 3) conducting management reviews; and 4) by ensuring the availability of necessary resources. The "legal and customer requirements" of a DRA are implicit in its Mandate – which may be an act, law or decree. In planning, the DRA must 1) ensure that quality objectives are established at the relevant functions and levels within the Agency; 2) ensure that quality objectives are measurable and consistent with the quality policy; and 3) ensure that planning for the QMS meets the general requirements (clause 4.1) and quality objectives (clause 5.4.1), as well as, maintains the integrity of the QMS. In as much as operations must be carried out the DRA must ensure that the responsibilities and authorities for such are defined and communicated appropriately. It is essential that a member of top management, irrespective of other duties, be appointed (as Quality Manager) and given the responsibility to: 1) ensure that the needed processes are established, implemented, and maintained; 2) report to top management on the performance of the QMS; 3) report to top management on any need for improvement; and 4) ensure the promotion of awareness of Agency's Mandate. Most DRAs have a public relation office. For a DRA to be effective it must review its QMS at planned intervals to: 1) ensure an effective QMS; 2) assess possible opportunities for improvement; 3) evaluate the need for any changes; and 4) consider the need for changes to the policy and objectives. The DRA must of course maintain records of reviews as per clause 4.2.4. For a DRA, the inputs for review must include information on: 1) results of audits; 2) feedback from government and the public, eg - incidences of counterfeit drugs; 3) status of preventive and corrective actions, eg – incidences of drug abuse; 4) follow-up actions from earlier reviews; 5) changes that can affect the QMS; and 6) recommendations for improvement.

Clause	Title and subtitles, with remarks	Salient points/ directing principles/ application to DRA
	changes that can affect the QMS, and recommendations for improvement.	
	5.6.3 Review Output - includes decisions/ actions related to: 1) improvement of the QMS; 2) improvement in meeting Mandate; and 3) resource needs	

*The Table is to be studied side by side with contents of ISO 9001:2008 and Table 2, which is on regulatory requirements of DRAs.

Table 6. Clause 5 of ISO 9001:2008 in relation to DRAs.

3.4.2. The immediate historical antecedent of NAFDAC and the continuing relevance of ISO 9001

Nigeria's NAFDAC was created by decree in 1992/93 following the ethylene glycol disaster of 1991/92 in Langtang General Hospital, Plateau State, where ethylene glycol was used in the place of propylene glycol in preparing paracetamol elixir. The glycol had been purchased from a hitherto popular pharmacy shop located at Masalachin-Jumai Street, Jos. Prior to 1992/93, a department in the Federal Ministry of Health handled food and drug administration in Nigeria. Alas, in 2009 another ethylene glycol disaster occurred in Lagos. In this latter disaster a hitherto popular brand of paediatric mixture ("My Pikin") was found to contain ethylene glycol that had been purchased from an unregulated source. It is important to note that whereas the glycol implicated in the Lantang disaster was purchased from pharmaceutically regulated source, the glycol in the case of the Lagos disaster was purchased from a company that dealt in industrial chemicals associated with automobiles and cooling systems. The occurrence of this kind of disaster within less than two decades is matter of concern that calls for a more efficient programme for regulating drugs and industrial chemicals in developing countries. The US-FDA after whose image and likeness NAFDAC was created is known for efficiency mostly because it is supported by proper laws and strong institutions. Better laws and stronger institutions, including DRAs, are required to avoid or minimize this kind of disaster as seen in Nigeria. It seems instructive to mention the "Tylenol case" in the US, and how that case led to a new legislation. Between late September and early October 1982, seven persons in Chicago died after taking capsules of Tylenol (a brand of paracetamol), to which cyanide crystals had been added. The crystals had apparently been introduced into the capsules by someone who had removed bottles of Tylenol from several drugstores and then replaced them on the shelves. It took an intensive investigation by a team of over 100 agents, including FDA staff, to discover the mischief, which led to a 1982-legislation that required all over-the-counter drugs and medicines sold in the county (and later elsewhere in the US and beyond) carry manufacturers' seals which broken would be obvious. The rapid conclusion of the investigation led by the Illinois Attorney General himself (Tyrone C. Fahner) and the dispatch with which the new law was issued collectively testify to the inner workings of strong institutions – which developing nations lack.

http://dx.doi.org/10.5772/50814

Clause	Title and subtitles, with remark	Salient points/ directing principles/ application to DRAs
6	**6 Resource management**	The DRA must determine and provide the resources needed: 1) to implement, maintain and continually improve the effectiveness of its QMS; and 2) to enhance the fulfilment of its Mandate.
	6.1 Provision of resources	
	6.2 Human resources	
	6.2.1 General	By virtue of its role as a highly specialized agency, the DRA must ensure that all staff irrespective of department whose work can impact DRA's Mandate are competent based on appropriate education, skills, experience and abide by their professional ethics.
	6.2.2 Competence, Training, and Awareness	
	6.3 Infrastructure	This implies that the DRA must: 1) determine the competency of staff; 2) provide training as needed; 3) evaluate the effectiveness of the actions taken on training and skills acquisition ; 4) inform staff of their relevance within the QMS; 5) ensure staff know their contributions to achieving quality objectives; and 6) maintain staff records of education, training, skill, and experience in accordance with clause 4.2.4.
	Like any other public outfit the DRA must determine, provide, and maintain infrastructure like buildings, workspace and associated utilities, and essential support services.	
	6.4 Work Environment	The DRA must, of course, provide appropriate work environment for all staff whose work impacts the DRA's Mandate.
	"Work environment" implies conditions under which work is performed, and includes physical aspects like weather and noise pollution.	

*The Table is to be studied side by side with contents of ISO 9001:2008 and Table 2, which is on regulatory requirements of DRAs.

Table 7. Clause 6 of ISO 9001:2008 in relation to DRAs.

3.4.3. The making of stronger DRAs and the need for clearer demarcation of responsibilities

In most countries where DRAs are not a department of the Ministry of Health, they exist as a parastatal or as a special department within the Ministry (as in Japan), with conditions of service being slightly more favourable than in the rest of the Ministry. The idea is to give special incentives to the staff on account of hazards perceived to be peculiar to the job. In Nigeria, NAFDAC is well housed both at the federal and state levels and the staff earn about the same remuneration as the universities and research institutes. In most countries the DRAs have well equipped offices and laboratories, and those DRAs that produce and distribute goods are equipped with the necessary plant and storage facilities.

3.4.4. The inevitability of confusion in the absence of regulatory standardization

In Nigeria, NAFDAC previously handled certain aspects of manufacture/ distribution of vaccines until certain developments (or rather controversies over quality/ effectiveness of polio vaccines during the late 1990s/ early 2000s) led, first to the creation of a National Programme on Immunization (NPI); and latter to the transfer of the same functions from NPI back to the Federal Ministry of Health. It is obvious from the foregoing that institutions like NAFDAC and NPI would have performed better had they been certified. It seems also that one of the keys to ending the cycle of poverty and underdevelopment in some countries is to ensure that elite institutions like the DRAs are certified to appropriate ISO standards. Certifications of agencies like the Health Insurance Scheme and the Pension Commission will definitely reduce perceive current levels of corruption in such institution.

Clause	Title and subtitles, with remark	Salient points/ directing principles / application to DRAs
7	**7 Product realization** **7.1 Planning of product** realization Product realization typically implies that manufacturers 1) plan and develop the QMS processes needed for product realization; 2) keep the planning consistent with other requirements of the QMS; 3) document the plan in a suitable form; and 4) determine through the planning, the following: a) quality objectives and product requirements; b) need for processes, documents, and resources; c) verification (establishment of truth/ confirmatory evidence), validation (formal registration/ obtainment of official sanction), monitoring, measurement, inspection, and test activities; d) criteria for product acceptance; and e) records providing evidence that the processes and resulting product meet requirements. Since DRAs regulate manufacturers they too must be acquainted with clause 7. NOTE 1: Recall that "quality plan" (2.4.8 of this article) is a document specifying the processes, and the resources to be applied to a specific product, project, or contract. NOTE 2: An organization can apply the requirements of sub-clause 7.3 (vide infra) to the development of product realization processes7.2 Customer-Related Processes **7.2.1 Determination of Requirements Related to the Product** **7.2.2 Review of Requirements Related to the Product** **7.2.3 Customer Communication** The intensity and scope of communication depends on the product and the associated mandate. Thus the DRA must determine and implement the necessary arrangements for communicating with stakeholders on aspects like 1) product information; 2) inquiries and contracts; 3) customer/ stakeholder feedbacks -positive or negative	Some DRAs produce/ store/ distribute specialized and non-profit products like vaccines and orphan drugs. For such, all aspects of clause 7 apply. The DRAs of developed economies concentrate on regulating manufacturers, distributors and use of products. Different processes are involved in drug regulation but these often have some aspects in common. For example, the process of registering a manufacturer and that of registering a product are essentially the same, but they differ in their aims, point of action, who by, and so on. Some of the processes involved in "planning of service realization", which is the core business of a typical DRA, require a wide range of differing concepts, technicalities, approaches, specializations, and so on. For example, although the technical aspects of producing tablets of aspirin, diazepam, B-complex, erythromycin, and orphan drugs may be similar, the modes of their regulation and distribution are different. Given the involved Mandate of DRAs, different strategies must be developed to grapple with the differing nuances and intricacies associated with the regulation of the five products. Typically, questions that have answer buried in culture/ society rather than the lab do arise in drug regulation. Why, for example, despite the similarities between NAFDAC and EMEA, it is impossible to buy erythromycin or diazepam over-the-counter in Europe but not in Nigeria? To what extent do political, social and economic factors affect "planning of service realization" in different social environments? It well known that regulatory strategies that work in Europe often fail to work outside despite obvious legislative similarities between nations. The customers/ stakeholders of a typical DRA are the general public, manufacturers, suppliers and the government. DRAs that engage in production and distribution must determine customer requirements, which invariably include specified and unspecified but desirable attributes. Such DRAs must also determine the legal requirements applicable to the product. Other desirable requirements, including post-delivery activities like maintenance services, may be considered. DRAs that produce or distribute would normally review the product requirements before committing to supply in order to: 1) ensure that product requirements are defined; 2) resolve any requirements differing from those previously expressed; and 3) ensure its ability to meet the requirements. In the same vein when a DRA plans a regulatory strategy or legislation the plan should be graduated and made reasonable to its purpose and scope and with reference to the operating socioeconomic environment. The DRA must maintain the results of reviews, and any subsequent follow-up actions in accordance with 4.2.4. When the requirements are not documented, they must be confirmed before acceptance. But if product requirements are changed, the DRA must ensure relevant documents are amended and relevant personnel are made aware of the changed requirements. NOTE: In some situations a formal review is impractical for each order. In such cases reviews can cover relevant product information such as catalogues or adverts.

*The Table is to be studied side by side with contents of ISO 9001:2008 and Table 2, which is on the regulatory requirements of DRAs.

Table 8. Clause 7 of ISO 9001 in relation to DRAs (Product planning and Customer-Related processes).

http://dx.doi.org/10.5772/50814

Clause	Title and subtitles, with remarks	Salient points/ directing principles/ application to DRAs
7	**7.3 Design and Development** **7.3.1 Design/ Development Planning** DRAs that produce or distribute must plan and control product design/ development. They must determine 1) the stages of design/development; 2) appropriate testing, review and validation for each stage; and 3) responsibility/authority for design/ development. **7.3.2 Design /Development Inputs** In designing/ developing a physical good or a service, the DRA must determine the needed inputs and keep records as per 4.2.4. The inputs must include: 1) functional and performance requirements; 2) applicable legal requirements; 3) applicable information derived from similar designs; and 4) requirements essential for design and development. **7.3.3 Design/ Development Outputs** Where applicable, DRAs must document the outputs of the design/ development process in a form suitable for verification against the inputs to the process. The outputs must 1) meet or match design and development input requirements; 2) provide information for purchasing, production and service; 3) contain or reference product acceptance criteria; 4) define essential characteristics for safe and proper use; 5) be approved before their release **7.3.4 Design/ Development Review** **7.3.5 Design/ Dev. Verification** **7.3.6 Design/ Dev. Validation** Validation activities are performed in accordance with 7.3.1 to confirm that the resulting product is capable of meeting the requirements for its specified application or intended use. **7.3.7 Control of Des./ Dev Changes** For either physical goods or policy, DRAs must 1) identify design and development changes and maintain records as per 4.2.4; 2) review, verify, validate and approve changes before implementation; 3) evaluate the changes in terms of their effect on constituent parts (raw material) and products (or policies) already delivered (or implemented).	The same principle followed in planning a physical product is followed in planning a service. The interfaces between the different groups involved must be managed to ensure effective communication/ clear assignment of responsibility. Design and development review, verification and validation have distinct purposes. They can be conducted and recorded separately or in any combination, as the DRA deems suitable for the product or the type of service. A DRA would review the selected inputs for adequacy and resolve any incomplete, ambiguous, or conflicting requirements. Examples of application inputs include: (1 applicable information derived from similar designs; and (2 requirements essential for design and development. If a DRA is designing a policy to curb drug abuse in a particular locality, useful inputs for the design would include statistics like 1) the age, gender and occupation of abusers; 2) the type of drugs abused; and 3) the success rate of similar policies elsewhere. NOTE: Information for production and service can include details for product preservation. A DRA must perform systematic reviews of design and development at suitable stages in accordance with planned arrangements (7.3.1) so as to: 1) evaluate the ability of the results to meet requirements; and 2) identify problems and propose necessary actions. Reviews must include representatives of the functions concerned. Results of reviews and subsequent follow-up actions must be maintained as per 4.2.4. A DRA would perform design and development verification in accordance with 7.3.1 to ensure that output meets the design and development input requirements; and maintain the results of such verification and subsequent follow-up actions. When practical and desirable, validation must be completed before delivery or implementation of the product. Results of the validation and of subsequent follow-up actions must be maintained as per 4.2.4. Just as some DRAs produce or distribute physical products, some DRA have their own testing facilities while others contract out such tests. Thus the purchase needs of DRAs differ with their Mandate. However, whenever purchasing is indicated the DRA must 1) ensure that purchased items conform to specified purchase requirements (Note: The type and extent of control applied to the supplier and purchased product depends upon the effect of the product on the subsequent realization processes or the final product); 2) evaluate and select suppliers based on their ability to supply goods in accordance with requirements; 3) establish the criteria for selection, evaluation, and re-evaluation; and 4) maintain the results of such evaluations and subsequent follow-up actions in accordance with sub-clauses 4.2.3 and 4.2.4.

*The Table is to be studied side by side with contents of ISO 9001:2008 and Table 2, which is on the regulatory requirements of DRAs.

Table 9. Clause 7 of ISO 9001:2008 in relation to DRAs (Design and Development).

3.4.5. Some causes and signs of a malfunctioning DRA

Once the staff recruitment system can be skewed to favour persons, a serious non-compliance exists. Once the purchase processes can be demonstrated to have vested interest, a serious flaw exists in the QMS. Once there is a convincing evidence of maladministration, arbitrary treatment of personnel or executive high handed, a serious condition against performance exists.

Clause	Title and subtitles, with remarks	Salient points/ directing principles/ application to DRAs
7	**7.4 Purchasing**	Whether a DRA produces/ distributes it will have cause to purchase various items of commerce
	7.4.1 Purchasing Process	hence QMS requirements for purchases are required. Like other organizations a DRA would
	7.4.2 Purchasing Information	require and ensure the adequacy of the specifications of items to be purchased before
	All organizations irrespective of type of business will have	communicating the purchasing information to the supplier. Typically a DRA would establish
	cause to purchase a multitude of goods for the business. If	and implement inspection or other necessary activities for ensuring that purchased goods
	such goods are to meet their purposes criteria and	meet the specified purchase requirements. If a DRA or its customers/ stakeholders propose to
	processes must be developed their purchase. Thus	verify a good or service at the supplier's location, the intended verification arrangements/
	purchasing information should contain: 1) explicit	method must be stated in the purchasing information.
	description of goods: 2) approval criteria for the goods,	It is typically pertinent that a DRA 1) validates any production or service provision that
	procedures, processes, and associated equipment or	subsequent monitoring cannot verify. Such validations include processes where deficiencies
	accessories; and 3) profession/ qualification of staff	may become apparent only after product use or service delivery; 2) demonstrates through the
	associated with the goods.	validation the ability of processes to achieve the planned results; and 3) establishes validation
	7.4.3 Verification of Purchased Product	arrangements including, as applicable: a) criteria for process review and approval, b) approval
	7.5 Production and Service Provision	of equipment, c) qualification of staff, d) use of defined methods and procedures, e)
	7.5.1 Control of Production and	requirements for records, and f) re-validation. DRAs that produce/ distribute or have their own
	Service Provision	test facilities must 1) identify, where appropriate, the product by suitable means during
	A producing/ distributing DRA must plan and carry out	product realization; and 2) identify the product status with respect to monitoring and
	production and service provision under controlled	measurement requirements throughout product realization. DRAs may require that
	conditions, which include: 1) availa-	manufacturers of herbal products have the following where necessary and feasible: a)
	bility of data on needed inputs; 2) availability of necessary	chemically defined reference active crude extract (RACE), b) chemically defined marker
	work instructions; 3) availability/ usability of essential	substance (DMS) and TLC, HPLC or GC-MS fingerprints of RACE and DMS. Since traceability is a
	equipment; 4) availability/ usability of monitoring and	key requirement, DRAs need to enforce manufacturers to have the means of controlling the
	measuring equipment; 4) ability to implement monitoring	unique identification of the product at various stages of development, and of course maintain
	and measurement	records.
	activities; and 5) ability to implement product release,	Obviously, DRAs that produce/ distribute products or run test laboratories/ facilities must
	delivery, and post-delivery activities. DRAs that	exercise care with any customer property under their control. They must record and promptly
	do not produce/ distribute must nevertheless have	report any loss or damage to the customer. NOTE: Customer property may be physical or
	possess the ability to ensure that manufacturer/	otherwise.
	distributors have all it takes to adequately meet	As a standard practice, a DRA would: 1) assess and record the validity of prior results if the
	QMS requirements.	equipment/ method are found not to conform to requirements; 2) maintain records of the
	7.5.2 Validation of Processes for	results of calibration and verification; and 3) confirm or re-confirm the ability of any software
	Production and Service Provision	or programme used for monitoring or measurement before its initial use. To ensure the validity
	7.5.3 Identification and Traceability	of results, a DRA would normally:
	7.5.4 Customer Property	1. Calibrate and/or verify the measuring equipment at specified intervals or prior to use.

http://dx.doi.org/10.5772/50814

Clause	Title and subtitles, with remarks	Salient points/ directing principles/ application to DRAs
	7.5.5 Preservation of Product	2. Calibrate the equipment to national or international standards (or record other appropriate
	Preservation of product broadly includes: 1) identification,	basis).
	2) handling,	3. Adjust or re-adjust as necessary.
	3) packaging, 4) storage, and 5) protection	4. Identify the measuring equipment in order to determine its calibration status
	7.6 Control of Measuring and	5. Safeguard equipment from improper adjustments.
	Monitoring Equipment	6. Protect equipment from damage and deterioration
	As may be applicable, a DRA would:	
	1) Determine the type of monitoring	
	and measurements to be made,	
	and the equipment/ method to be	
	used in providing evidence of conformity	
	2) Use and control the monitoring and measuring devices	
	in order to ensure that measurement capability is	
	consistent with monitoring and measurement	
	requirements.	

*The Table is to be studied side by side with contents of ISO 9001:2008 and Table 2, which is on the regulatory requirements of DRAs.

Table 10. Clause 7 of ISO 9001:2008 in relation to DRAs (Purchasing/ Production/ Control of Equipment).

Clause	Title and subtitles, with remarks	Salient points/ directing principles/ application to DRAs
8	**8 Measurement, analysis and**	Given the overwhelming importance of measurement, analysis and improvement to the
	Improvement	Mandate of DRAs, a DRA would typically want to be sure, thorough and effective in the
	8.1 General	application of clause 8. To ensure effectiveness therefore, the DRA would routinely, or as may
	A producing/ distributing DRA would plan and implement	be necessary, determine through planning the need for, use of, and extent of use of applicable
	the monitoring, measurement, analysis, and improvement	methods, including statistical techniques. DRAs should view customer/ stakeholder perception
	processes it needs to: 1) demonstrate conformity to	as a key performance measurement of its QMS. For producing and/ or distributing DRAs
	product requirements; 2) ensure conformity of the QMS	especially, monitoring customer/ stakeholder perception can be obtained from: 1) customer/
	to planned arrangements;	stakeholder satisfaction surveys; 2) customer data on delivered product quality; 3) user opinion
	and 3) continually improve the effectiveness of the QMS.	surveys; 4) lost business analysis; 5) compliments; 6) warranty claims; and 7) dealer reports.
	Non-producing/ distributing DRAs	For thoroughness and effectiveness a producing/ distributing DRA must: 1) plan the audit
	must have the ability to ensure that manufacturers/	program; 2) consider the status and importance of the audited areas; 3) consider the results of
	distributors comply.	prior audits; 4) define the audit criteria, scope, frequency, and methods; and 5) select and use
	8.2 Monitoring and measurement	impartial and objective auditors. Non-producing/ distributing DRAs must have the ability to
	8.2.1 Customer Satisfaction	ensure that manufacturers/ distributors comply.
	DRAs must routinely: 1) monitor information on	To institute thoroughness and effectiveness, producing/ distributing DRAs must:
	customer/ stakeholder perception as to whether it is	1. Maintain records of the audits and their results.
	meeting	2. Ensure control of the audited areas.
	its Mandate; and 2) define the	3. Take actions without undue delay to eliminate detected nonconformities and their causes.
	methods for obtaining and using that information.	4. Verify through follow-up actions.
	8.2.2 Internal Audit	

Clause	Title and subtitles, with remarks	Salient points/ directing principles/ application to DRAs
	Internal audits must be conducted at planned intervals so that DRAs can determine if their QMS: 1) conforms to requirements of ISO 9001:2008; 2) conforms to planned arrangements as per sub-clause 7.1; and 3) is effectively implemented and maintained. In order to thoroughly address staff responsibilities and the requirements to be met by the audit exercise, DRAs must establish: 1) a documented procedure for planning audit; 2) a documented procedure for conducting audits; and 3) a documented procedure for recording and reporting audit results.	Again, non-producing/ distributing DRAs must have the ability to ensure that manufacturers/ distributors comply. NOTE: ISO 19011 (Audit guidance) should be consulted for further enlightenment quality auditing.

*The Table is to be studied side by side with contents of ISO 9001:2008 and Table 2, which is on the regulatory requirements of DRAs.

Table 11. Clause 8 of ISO 9001:2008 in relation to DRAs (Monitoring and measurement).

3.4.6. Remediation of a malfunctioning DRA

A national or regional DRA is a critical factor in socioeconomic development and wellbeing in at least two ways: i) by "guaranteeing the health of the nation" (as trumpeted in NAFDAC's adverts); and by supporting the emergence of responsible manufacturers of regulated products. It is well known that the US-FDA more than any US organization has made the US the world leader in manufacture of health products. The prominence of India and China in world drug trade owes much to the vibrancy and relative efficiency of their DRAs. There is therefore a critical need for DRAs to be vibrant and responsible. The gravity with which China views the role of her DRA can be gauged by the death sentence passed on the Director General in 2007 for accepting a bribe [15].

Clause	Title and subtitles, with remarks	Salient points/ directing principles/ application to DRAs
8	**8.2.3 Monitoring and Measurement of Processes** 1) Apply suitable methods to monitor and, where applicable, measure the QMS processes. 2) Confirm through these methods the continuing ability of each process to satisfy its intended purpose. 3) When the planned results are not achieved, take correction and corrective action, as appropriate. **8.2.4 Monitoring and Measurement of Product**	Producing/ distributing DRAs need to 1) apply suitable methods for monitoring and measuring QMS processes; and 2) confirm through these methods the continuing ability of each process to satisfy its intended purpose. Non-producing/ distributing DRAs must have the ability to ensure that manufacturers/ distributors comply. NOTE: When determining "suitable" methods, consideration is given to the type and extent of monitoring or measurement for each process in relation to its impact on product conformity and on the effectiveness of the QMS. To better fulfil their Mandate producing/ distributing DRAs must 1) monitor and measure product characteristics so as to verify if product requirements are being met; 2) carry out the monitoring and measurements at the appropriate stages of product realization in accordance with planned arrangements; and 3) maintain evidence of conformity with the acceptance criteria.

http://dx.doi.org/10.5772/50814

Clause	Title and subtitles, with remarks	Salient points/ directing principles/ application to DRAs
	1) Monitor and measure product characteristics to verify if product requirements are being met. 2) Carry out the monitoring and measuring at the appropriate stages of product realization in accordance with planned arrangements (see 7.1). 3) Maintain evidence of conformity with the acceptance criteria. 4) Record the person responsible for authorizing release of product for delivery to the customer.	It is again stressed that non-producing/ distributing DRAs must have the ability to ensure that manufacturers/ distributors comply. DRAs must ensure that product release and service delivery cannot proceed until all planned arrangements (see 7.1) have been satisfactorily completed, unless otherwise approved by a relevant authority, and where applicable, the customer. Where applicable, DRAs must deal with the nonconforming product by one or more of the following ways: 1. Take action to eliminate the detected nonconformity. 2. Authorize its use, release, or acceptance by concession. 3. Take action to preclude its original intended use or application. 4. Take action appropriate to the effects, or potential effects, of the nonconformity when nonconforming product is detected after delivery or use has started
	8.3 Control of nonconforming product DRAs must: 1) Ensure any nonconforming product is identified and controlled to prevent its unintended use or delivery. 2) Establish a documented procedure to define the controls and the related responsibilities/authorities for dealing with nonconforming product. DRAs must maintain records of the nature of the nonconformity, and any subsequent actions, (including any concessions). When the nonconformity is corrected, DRAs must re-verify it to prove or show evidence of conformity.	To better fulfil their Mandate, DRAs must: 1) Ensure that any nonconforming product is identified and controlled to prevent its unintended use or delivery. 2) Establish a documented procedure to define the controls and related responsibilities and authorities for dealing with nonconforming product.

*The Table is to be studied side by side with contents of ISO 9001:2008 and Table 2, which is on the regulatory requirements of DRAs. Although a DRA may not possess certain facilities for measurements and monitoring, it should possess the ability or the means necessary to ensure that manufacturers/ distributors possess and use them in accordance with approved QMS guidelines.

Table 12. Clause 8 of ISO 9001 in relation to DRAs (Product characteristics/ Control of nonconformities).

In Nigeria, the entire NAFDAC Management was sacked on alleged acts of corruption in 2000. It seems to us that the following are essential for a DRA to perform optimally:

1. The laws creating/ amending a DRA should be well articulated as is the case with the US-FDA.
2. DRAs should be so well funded as not to rely on a plethora of frivolous fees as with NAFDAC.
3. Staffing of DRAs must be transparent - competence and integrity must be the decisive criteria.
4. DRAs should be audited frequently, at least yearly or twice yearly.
5. DRAs should have a Board of Governors to whom the Management reports.

6. Parliamentary health committees should view DRAs as critical to socioeconomic well-being of the nation.

Clause	Title and subtitles, with remarks	Salient points/ directing principles/ application to DRAs
8	**8.4 Analysis of data**	DRAs should as a matter of practice:
	Whether producing/ distributing or not, as a rule,	1. Include the primary data generated by monitoring and measuring activities, and from other
	DRAs must determine, collect, and analyze appropriate	relevant sources in their analyses.
	data to demonstrate the suitability and effectiveness of	2. Analyze such primary data to provide secondary data on:
	their QMS, as well as, evaluate where continual	a. Customer satisfaction as per 8.2.1.
	improvement of the QMS can be made.	b. Conformity to product requirements as per 8.2.4.
	DRAs cannot enforce compliance among	c. Characteristics and trends of processes and products, including opportunities for preventive
	manufacturers/ distributors in an aspect of quality	action as per 8.2.3, 8.2.4, and 8.5.3.
	management in which they are themselves deficient.	d. Suppliers as per 7.4
	8.5 Improvement	DRAs are to continually improve the effectiveness of their QMS through:
	8.5.1 Continual Improvement	1. Quality policy
	8.5.2 Corrective Action	2. Quality objectives
	The standard practice for organizations is that:	3. Audit results
	1. Wherever a nonconformity or breach is detected,	4. Analysis of data
	corrective action must be taken to eliminate the cause	5. Corrective and preventive action
	of the nonconformity and to prevent its recurrence.	6. Management review
	2. Wherever corrective action is taken by an	For thoroughness and effectiveness, DRAs must establish a documented procedure (SOP) for
	organization, such action must be such as is	corrective action. Such a procedure must define requirements to:
	appropriate to the	1. Review nonconformities (including customer complaints).
	effects of the problem caused by the nonconformity or	2. Determine the causes of nonconformities.
	breach.	3. Evaluate the need for actions to prevent recurrence.
	8.5.3 Preventive Action	4. Determine and implementing the needed action.
	Organizations must:	5. Maintain records of the results of the action taken.
	1. Determine in advance the action	6. Review the effectiveness of corrective action taken
	that needs to be taken to eliminate	For thoroughness and effectiveness, DRAs must establish a documented procedure for
	the causes of potential non-	preventive action. Such a procedure must define requirements to:
	conformity, in order to prevent its occurrence.	1. Determine potential nonconformities and their causes.
	2. Ensure that preventive actions are appropriate to	2. Evaluate the need for actions to prevent occurrence.
	the anticipated effects of the potential problem.	3. Determine and implementing the needed action.
		4. Maintain records of the results of the action taken.
		Review the effectiveness of preventive action taken

*The Table is to be studied side by side with contents of ISO 9001:2008 and Table 2, which is on the regulatory requirements of DRAs. It must be stressed once again that if DRAs are to persuade manufacturers/ distributors to comply with the provisions of this and other clauses of ISO 9001:2008 industrial standard, they too must be conversant with and adept in them.

Table 13. Clause 8 of ISO 9001:2008 in relation to DRAs (Analysis of data/ Improvement).

http://dx.doi.org/10.5772/50814

3.4.7. Further remarks on clauses 7 and 8 of ISO 9001:2008

Although the principles of clauses 7 and 8 apply to all organizations, they are strictly speaking, the deeds and stuff intended for high profile institutions with elaborate concern and facilities for design and R&D, and with tall entrepreneurial ambition. Such organizations include the most successful pharmaceutical and biotechnology companies of the US, Europe, Japan and India; NASA, aircraft manufacturers, international airlines and 5-star hospitality concerns. However, in as much as DRAs must regulate the work and product of advanced pharmaceutical manufacturers, the onus is upon the DRAs themselves to be conversant with the entire provisions of these clauses and be as intellectually equipped as the manufacturer. This explains why it is often desirable that regulators have a stint in both academia and industry. In many countries, especially the US and India, top rate biomedical facilities/ institutions and personnel are to be found in the following four circles: i) the DRAs (eg: US-FDA); ii) health research institutions (eg: NIH); iii) the universities/ R&D institutions patronized by the DRAs; and iv) big transnational drug manufacturers (eg: Pfizer). We once again refer to the Nigeria polio vaccine controversy of the late 1990s/ early 2000s mentioned earlier, and ask the following question: When a DRA produces or distributes product as is the case in many developing economies, who regulates the DRA? Can subsequent revisions of ISO 9001or some other ISO standard provide an answer?

4. Conclusions

It is evident from the foregoing that all the eight clauses of ISO 9001:2008 apply to the Mandate of DRAs. However, most of what appears in clauses 7 and 8, the lengthiest of the clauses, relates more pertinently to high stake pharmaceutical manufacturers that have elaborate R&D than they do to the average DRA, which nevertheless should be thoroughly acquainted with the clauses. Some DRAs like the US-FDA and EMEA that have advance laboratories or access to such or that heavily fund R&D must be guided by the rigorous provisions of clauses 7 and 8. Needless to say, those DRAs that produce/ distribute products must be similarly guided to the extent of their relevance to the scope and size of their operations. The US-FDA, Japan's Ministry of Health and Social Services and EMEA are certified to appropriate performance standards and are known for their efficiency. By contrast NAFDAC and other developing national DRAs are not similarly certified and are less well known for efficiency, considering the rampancy of counterfeit drugs and other ills in their drug delivery systems. The DRAs of China, India and Southeast Asian countries compare quite well in many aspects with those of Europe, Canada and the US, and are by far more efficient than those of many African and South American countries. From the foregoing, and in view of the historical and international dimensions of phytotherapy, especially its galloping global patronage in recent times [1,2,11,12], it is necessary that there to be a minimum global standard to which DRAs should be certified. We propose ISO 9001 because of its global popularity, applicability and suitability. The standard provides the general climate for DRAs to efficiently discharge their Mandate. We project that a carefully planned application of ISO 9001 to herbal drug regulation will improve the production, distribution and usage of herbal drugs.

It will also boost the economy of developing economies that rely to a large extent on herbal drugs. But since the DRAs of many developing economies produce/ distribute certain products, there is a need for subsequent revisions of ISO 9001 to take cognisance of the question of who regulates the regulator that produces/ distributes? In the meantime we recommend that the Minister/ Secretary of Health and/ or the Parliamentary Committees of Health take note of this significant lacuna.

Acknowledgements

We gratefully acknowledge a copy of ISO 9001:2008 kindly furnished by the SON and the enlightenment offered by Engineer Timothy N. Abner, Dr. Justin B. Nickaf and Engineer. Shehu I. Maik during the NIPRD-SON workshop on ISO 9001:2008 held at Bolton White Apartments, Abuja, in November-December 2011.

Author details

Sunday Ameh[1*], Florence Tarfa[1], Magaji Garba[2] and Karniyus Gamaniel[3]

*Address all correspondence to: sjitodo@yahoo.com

1 Department of Medicinal Chemistry & Quality Control, National Institute for Pharmaceutical Research and Development (NIPRD), Idu Indusrial Area, Nigeria

2 Department of Pharmaceutical & Medicinal Chemistry, Ahmadu Bello University, Nigeria

3 Office of the Director General, NIPRD, Idu Indusrial Area, Nigeria

References

[1] Ameh, S. J., Obodozie, O., Inyang, U., Abubakar, M., & Garba, M. (2010). Current phytotherapy- a perspective on the science and regulation of herbal medicine. *Journal of Medicinal Plants Research*, 4(2), 072-081.

[2] Ameh, S. J., Obodozie, O., Inyang, U., Abubakar, M., & Garba, M. (2010). Current phytotherapy- an inter-regional perspective on policy, research and development of herbal medicine. *Journal of Medicinal Plants Research*, 4(15), 1508-1516.

[3] Ameh, S. J., Obodozie, O., Gamaniel, K., Abubakar, M., & Garba, M. (2011). Herbal Drug Regulation Illustrated with Niprifan® Antifungal Phytomedicine.

In: Eldin AB, editor. Modern Approaches to Quality Control, Rijeka, InTech, 367-382.

[4] DSHEA (1994). Dietary Supplements Health Education Act of 1994. Available: http://fda/Food/DietarySupplements/ucm109764.htm Accessed 2012 April 25.

[5] Goldman, P. (2001). Herbal medicines today and the roots of modern pharmacology. *Ann. Int. Med.*, 135(8), Pt 1, 594-600.

[6] Chineseherbsdirect.com (2010). What are Chinese Herbs? Available: http://www.chineseherbsdirect.com Accessed 2012 April 25.

[7] EDTHMP (2004). European Directive on Traditional Herbal Medicinal Products. Available: http://eur-lex.europa.eu/LexUriserv/LexUriserv.do?uri=CELEX:32004L0024:EN:NOT Accessed 2012 April 25.

[8] De Smet, P. (2005). Herbal medicine in Europe- relaxing regulatory standards. *N. Eng. J. Med.*, 352(12), 1176-78.

[9] Mapdb.com (2003). Current status of medicinal plants. Available: http://www.mapbd.com/cstatus.htm Accessed 2012 April 25.

[10] WHO. (2008). Traditional Medicine. *WHO Fact sheet* [134], Revised: December World Health Organization, Geneva.

[11] Ameh, S. J., Obodozie, O. O., Chindo, B. A., Babalola, P. C., & Gamaniel, K. S. (2012). Herbal clinical trials - historical development and application in the 21st Century. Pharmacologia . DOI: 10.5567/pharmacologia.2012.121.131 Accessed 2012 April 25., 3, 121-131.

[12] Ameh, S. J., Obodozie, O. O., Babalola, P. C., & Gamaniel, K. S. (2011). Medical Herbalism and Herbal Clinical Research - A Global Perspective. *British Journal of Pharmaceutical Research*, 1(4), 99-123.

[13] Juran, J. M., & Godfrey, A. B. (1999). *Juran's Quality Handbook: The Complete Guide to Performance Excellence* (5th Edition), McGraw-Hill Professional, New York, USA, 1-1872.

[14] Pyzdek, T. (2003). Quality Engineering Handbook. 2nd Edition (Ed. Keller, P.), CRC Press, New York, USA, 1-744.

[15] ISO Survey (2009). Available: http://www.iso.org/iso/survey2009.pdf Accessed 2012 April 25.

[16] Ann Godsell Regulatory (2008). Pharmaceutical Good Manufacturing Practice for Herbal Drug Substances 2008 [cited 2010 April 8]. Available: http://www.pharmaceutical-int.com/article/category/treatment-herbal-medicines Accessed 2012 April 25.

[17] Akunyili, D. (2002). Herbal Preparations. *NAFDAC Consumer Safety Bulletin*, 1(2), 5-6.

[18] Gross, A., & Minot, J. (2007). Chinese Manufacturing: Scandals and Opportunities. Published in MX, November/ December, Pacific Bridge Medicals. Available: http://www.pacificbridgemedicals.com/ Accessed 2012 April 25.

[19] Corbett, C. J., Montes-sancho, M. J., & Kirsch, D. A. (2005). The financial impact of ISO 9000 certification in the United States: An empirical analysis. Management Science Available: http://personal.anderson.ucla.edu/charles.corbett/paper/does_iso_pay.pdf Accessed 2012 April 25., 51(7), 1046-1059.

[20] Heras, I., Dick, G. P., & Casadesus, M. (2002). ISO 9000 registration's impact on sales and profitability - A longitudinal analysis of performance before and after accreditation. International Journal of Quality and Reliability Management Available: http://eps.udg.es/oe/webmarti/p774.pdf Accessed 2012 April 25., 19(6), 774-791.

[21] Naveh, E., & Marcus, A. (2007). Financial performance, ISO 9000 standard and safe driving practices effects on accident rate in the U.S. motor carrier industry. Accident Analysis & Prevention PMID 17166474Accessed 2012 April 25., 39(4), 731-742.

[22] Sharma, D. S. (2005). The association between ISO 9000 certification and financial performance. The international Journal of Accounting Available: http://masp.bus.ku.ac.th/files/ISO%209000%20and%20performamce.pdf Accessed 2012 April 25., 40, 151-172.

[23] Chow-chua, C., Goh, M., & Wan, T. B. (2002). Does ISO 9000 certification improve business performance? The International Journal of Quality & Reliability Management Available: http://www.emeraldinsight.com/journals.htm?articleid=840633&show=abstract Accessed 2012 April 25., 20(8), 936-953.

[24] Rajan, M., & Tamimi, N. (2003). Payoff to ISO 9000 registration. Available: http://www.iijournals.com/doi/abs/10.3905/joi.2003.319536Accessed 2012 April 25.