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HERBAL PRODUCT REALIZATION IN ACCORDANCE WITH WHO AND ISO GUIDELINES

S. J. Ameh*, F. Tarfa, S. Ayuba, K. S. Gamaniel

Department of Medicinal Chemistry and Quality Control (MCQC) [1], National Institute for Pharmaceutical Research and Development (NIPRD), Idu Industrial Area, PMB 21 (Garki), Abuja, Nigeria

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Correspondence to Author:

S. J. Ameh

Department of Medicinal Chemistry and Quality Control (MCQC) [1], National Institute for Pharmaceutical Research and Development (NIPRD), Idu Industrial Area, PMB 21 (Garki), Abuja, Nigeria

Email: sjitodo@yahoo.com

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ABSTRACT

Background: Following the Alma-Ata Declaration of 1978, the World Health Organization (WHO) began the issuance of guidelines for developing standardized herbal preparations from Traditional Medicine (TM). Similarly in 1987, the International Organization for Standardization (ISO) launched the most anticipated industrial standard (ISO 9001) in world history. The seventh (7^{th}) clause of ISO 9001's eight clauses is devoted to "Product Realization"- a quality management system (QMS) procedure that includes: planning of product realization; appreciation of customer-related processes; design and development processes; purchasing; production and service provision; and control of measuring and monitoring equipment.

Purpose: The article takes a hard look at the QMS processes involved in product realization and the critical stages of the WHO model of herbal drug development from TM, with a view to devising a framework that can be used to promote the production of quality herbal products, commencing from the stage of ethnobotanical survey, through the laboratory, to the clinic.

Methodology: Both the WHO model of herbal drug development and the 7^{th} clause of ISO 9001:2008 were critically reviewed and combined to yield a framework that is discussed within the context of guiding herbal drug development from TM.

Results and Discussion: The resulting WHO-ISO framework of herbal product realization is discussed in terms of its relevance to practical problems of GMP-production using herbal starting materials, given their innate variability in composition, potency and appearance.

Conclusion: The provisions of ISO 9001's seventh clause can, to a large extent, be applied to the production of quality herbal products developed in accordance with WHO.

INTRODUCTION: Medicinal herb or "herbal substance" is also called herbal drug among other synonyms by WHO [1], European Pharmacopoeia [2] and others [3]. Typically, it is a plant preparation derived from one or more parts, such as the leaves, flowering parts, stem or root bark or whole stem or root, based on established herbal tradition. WHO[1] defined "herbal substance" as: "material derived from plant by extraction, mechanical manipulation, or some other process". The term specifically applies to whole preparations not isolated or purified components thereof. In herbological terminology each "herbal substance" from a given plant is in its entirety regarded as the active substance, even though the preparation may contain several

chemically defined entities [4]. This is because it is conceived that the entities act cooperatively to achieve the pharmacological attribute of the plant. The practice of preparing herbal cocktails is termed "chemistry-manufacturing-control" (C-M-C) by WHO [1], because it involves an understanding of physicochemical processes and how to control them.

The C-M-C of a given "herbal product", defined by WHO[1] as an "herbal material administered to clinical subjects", focuses on the fact that herbal substances are prone to contaminations by herbicides, pesticides, mycotoxins and others [5] and are subject to profound variations in physicochemical characteristics [6, 7], such as moisture content, ash values, extractability and others [8]. The cultivation, harvest, contaminations, process history and the physicochemical characteristic of an herbal substance are critical to its C-M-C evaluation, if good manufacturing practice (GMP) is to be applied in producing an herbal product [8, 9].

The methodology section of this article examined WHO guidelines on herbal drug research and development (R&D); and the parameters for "product realization" according to ISO 9001:2008, with a view to developing a conceptual framework that can be used to guide research, development and quality production of herbal products.

METHODOLOGY

1. **WHO Model of Herbal Drug Development:** The WHO approach to herbal drug development is spelt out in the following documents:

i) Research guidelines for evaluating the safety and efficacy of herbal medicines [7];

ii) The manual on quality control methods for medicinal plant materials [6];

iii) General guidelines on methodologies for research and evaluation of tm [5]; and

iv) The 16-page document on information needed to support herbal clinical trials [1].

a) **WHO manual on Quality Control Methods for Medicinal Plant Materials:** The manual contains a long list of tests/ procedures that includes the comparison of medicinal plant materials or products with suitable standards to determine whether they should be accepted, rejected or reworked. The term "standards" implies that certain procedures need to be established for such tests, measurements and comparisons. The International Pharmacopoeia by WHO is copiously referenced by the manual. Some of the WHO procedures most commonly utilized in NIPRD includes: macroscopic and microscopic examinations; physicochemical tests like loss on drying, ash values and water extractability, bitterness, foaming index and so on; some basic tests for primary and secondary metabolites; and chromatography, especially TLC, but HPLC, GC-MS and other more advanced chromatographic techniques are also practised. Tests involving spectroscopy, such as light and atomic absorption, as described in the manual or in the WHO pharmacopeia are also applied in NIPRD. Some specific key features/ prescriptions of the manual are as follows:

b) Calculation of Results and Statistical Analysis:

i. Rounding up or down: Results of tests, assays or standardizations of Volumetric Standards (VS) are calculated to one decimal place more than indicated in the requirement and then rounded up or down. Examples: 12.45 to 12.49 become 12.5. 1.340 to 1.344 becomes 1.34.

ii. Calculation of values such as loss on drying, total ash extractable matter, etc. etc. These must be calculated with reference to the air-dried sample, usually as %w/w, unless otherwise stated.

iii. Statistical analysis: Student's "t" distribution may be used as a test of the null hypothesis. The levels of significance may be set at 0.05, 0.01 and 0.001 corresponding to 95%, 99% and 99.9% confidence limits.

c) **Conditions of Storage:** These are specified in accordance with the following:

i. Containers and enclosures: These must not interact with the material. The following types were specified.

1) Well-closed container: protects the content from extraneous matter or from loss of material under, normal conditions of handling, shipment or storage.

2) Tightly-closed container: protects the content from extraneous matter, from loss of material, and from efflorescence, evaporation, or deliquescence, under normal conditions of handling, shipment or storage.

ii. **Protection from light**: This is achieved either by using an opaque container, or by shielding the container with light-resistant coverings, or by storage in a dark place.

d. **Size of Cut:** Cut materials, where necessary, are graded according to the aperture size of mesh through which the materials pass, as follows:

Description	Aperture Size [mm]
Coarse cut	4.00
Medium cut	2.80
Fine cut	2.00

e. **Sampling:** Sampling is so critical in medicinal plants research that elaborate procedures are required, especially because medicinal plant materials generally lack homogeneity (**table 1**). The questions that may arise are: What special handling procedures are required? Which parts of the plant are to be included in the sample? These are addressed as follows:

i. Sampling of Materials in Bulk: First, each container is inspected to ascertain conformity with prescribed packaging and labelling. Checks are made for damaged or poorly labelled containers, and where necessary these are sampled individually and separately. Second, if the rest of the batch is uniform, containers are selected for sampling as shown in **Table 2**.

TABLE 1: SAMPLING OF MATERIALS IN BULK AS PER WHO (1998)

Number of containers per batch	Number of containers to sample	Remark
1 – 5	Each	-
6 – 50	5 selected at random	-
51 and above	10% selected at random	51 are treated as 60. 61 are treated as 70, etc. etc.

Third, the selected containers are opened, and the contents are examined, looking out for the characteristics stated in **Table 2**.

TABLE 2: CHARACTERISTIC TO LOOK FOR IN SAMPLES SUPPLIED IN BULK

General Characteristics.	Specific Example of Characteristics
Organoleptic	Color, texture, odor, etc. etc.
Form of presentation	Raw, cut, crushed, compressed, etc.
Presence of admixture/ foreign matter/ mould/ signs of decay.	Sand, glass particles, dirt, etc. etc.
Presence of insects.	
Presence of packaging material originating from poor or degraded containers.	Note type, as it may indicate a significant finding. Note type, as it may indicate a significant finding.

Fourth, the following points/actions are taken note/ carried out in the actual act of sampling:

1) Three (3) original samples from each container – from: top, middle and bottom are taken.

2) The 3 original samples are combined into a pooled sample and mixed carefully.

3) The average sample is obtained by "quartering" the pooled sample. b. Quartering

ii. Quartering consists of the following steps:

a) A pooled sample from original samples is mixed carefully and thoroughly, and constituted it into a square-shaped heap.

b) The heap is divided diagonally into 4 equal parts, and any 2 diagonally opposite parts are selected and mixed carefully.

c) The process is repeated as necessary until the required quantity of sample is obtained.

d) Any remaining material is returned to the batch.

iii. Final samples: Final samples are obtained from an average sample by quartering, as described above. This means that an average sample gives rise to 4 final samples. Each final sample is divided into 2 portions. One portion is retained as reference material, while the other is tested.

f. **Establishment of limits:** Where possible or necessary analytical results from 20 successive batches are pooled together, and the grand mean and "three sigma limits" (± 3 Standard Deviations) are calculated, to represent established limits.

g. **Harvesting/ collection and drying of aerial parts:** Aerial parts are harvested in the mornings by cutting the plant at least 1 cm above ground level with the aid of sharp scissors. The parts are routinely shaken to remove dust, dead parts and unwanted debris and foreign matters. The parts may be treated with running potable water to remove unwanted items. Subsequently, the parts are dried in a shade by placing them on stainless steel mesh or by any other suitable means. The materials are considered sufficiently dry once they are brittle to touch and amenable to grinding with an electrically powered grinding machine.

h. **Harvesting/ collection and drying of underground parts:** Underground parts are harvested in the mornings by digging out the system underground and cutting off portions thereof with a sharp cutlass or axe. The parts are routinely treated with running potable water to remove unwanted soil particles. Subsequently, the parts are cut into manageable bits and dried in a shade by placing them on stainless steel mesh or by any other suitable means. The materials are considered sufficiently dry once they become brittle and amenable to grinding with an electrically powered grinding machine.

i. **Examination of fresh or air-dried materials:** Examinations of materials for purposes of authentication are based on visual inspection, including microscopy, to establish shape, size, colour, texture, and appearance of cut surfaces. Odour and taste, called organoleptic characteristics, are also used in identification. Items usually required include devices for measurements including: ruler, graph paper, caliper, micrometer screw-gauge, razor blade or scalpel, and hand lens or microscope may be used to determine shape and size.

j. **Tests for primary and secondary metabolites:** The manual provide detailed chemical microscopy especially for primary metabolites. Tests for secondary metabolites (phytochemicals) may be performed according to standard procedures as described elsewhere. Such tests, as described and applied elsewhere [10-15] in related studies, include: Dragendorff's test for alkaloids; Borntrager's test for anthraquinones; Keller-Killani's test for cardiac glycosides; Foaming test for saponins; Aqueous $FeCl_3$ test for tannins; and Salkowaski's test or Libermann-Burchad test for terpenoids/ steroids.

2. WHO guidelines on safety and efficacy of herbal drugs and research on TM: The 1993 WHO document [7] containing the guidelines for conducting scientific research on the safety and efficacy of herbal medicines (HMs) reflect the consensus reached by 17 experts in pharmacology, biochemistry, and TM. The guidelines respond to the need to assure the safety of widely used HMs while also facilitating the search for new pharmaceutical products. Specific research criteria are covered together with general principles of investigation, including ethical concerns. The document has three parts.

The first discusses the special properties of herbal medicines that need to be considered when designing research protocols.

The second part provides detailed guidance on the objectives of research, the contents of a research protocol, and the methods of investigation for non-clinical studies and for Phase I to Phase IV clinical trials.

The third part, which forms the core of the book, presents three sets of research guidelines: for quality specifications of plant materials and preparations, for pharmacodynamic and general pharmacological studies of HMs, and for toxicity investigation of HMs.

Topics covered range from the information required to establish the identity and quality of plant materials or preparations, through the selection of appropriate test systems for pharmacodynamic studies, to detailed advice on the many different tests, examinations, observations, and experimental procedures required, in experimental animals and controls, to establish the safety of herbal medicines. The guidelines are intended to facilitate the work of research scientists and clinicians while also furnishing some reference points for the governmental, industrial, and non-profit organizations providing financial support. The 2000 WHO document [5] on research methodologies on TM is mostly an update of 1993 document on essentially the same subject [7], but incorporating aspects of non-herbal TM. Key conclusions on aspects of documentation of safety of use of herbal drugs based on TM experience are shown in **Table 3**.

TABLE 3: DOCUMENTATION OF SAFETY OF USE OF HERBAL DRUGS BASED ON TM EXPERIENCE

State of affairs / knowledge of safety	The type of action that needs to be taken
No toxicological data exist	Documented experience of long-term use of at least 20-30 years without untoward effects should form the basis of risk assessment.
Some toxicological data exist	(a) The period during which the drug had been in use should be noted. (b) The health disorder treated with the drug should be noted. (c) The number of patients so treated should be noted. (d) The location in which the treatment was carried out should be noted.
There is toxicity	(a) Attempts must be made to establish its dose-dependency. (b) Attempt must be made to explain (a) above.
There is potential for misuse	All cases of abuse or dependence must be documented.
Long-term use cannot be proved	Attempts must be made to conduct toxicity studies

The above was prepared based on guidelines provided by WHO[7] regarding the documentation of the safety of use of an herbal drug based on traditional experience, as elaborated upon elsewhere[16-19].

3. Information needed to support herbal clinical trials: We earlier (Ameh *et al.,* 2011) emphasized that drug development from a traditional herb can take the route of standardization of the herb or its extract for immediate use without further chemical manipulations. Standardization in this sense implies there is sufficient chemical data for identifying the herb, for processing the herb, and for controlling the processes. In other words there is sufficient C-M-C data [1] to produce the "herbal product" – namely: an "herbal material administered to clinical subjects" (WHO, 2005b). In the 2008 Annual Lecture of the Nigerian Academy of Science, Professor Wambebe [20] (formerly Dean, Faculty of Pharmaceutical Sciences, ABU, Zaria and the first Director General of NIPRD) had made the following pertinent comment on "Drug Development Chain":

"A simplified drug development chain encompasses discovery phase…Traditional medicine belongs to the discovery phase in that chain. If a proper ethnomedical survey is conducted accompanied by clinical observational study following WHO guidelines, it is possible to save substantial funds and drastically reduce the time needed to obtain credible data…." Wambebe [20]. The logic of the position follows directly from the reasoning provided in the aforesaid references [1, 5, 7].

4. Synopsis on ISO 9001:

a. **ISO 9001 as an industrial standard:** ISO 9001 as an industrial standard or QMS is a document of about 30 pages with 8 clauses, published by ISO and obtainable from its headquarters in 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 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 or approaches (often called "QMS requirements" or "quality procedures") are generic and are intended to be applicable to every organization irrespective of type, size and product it provides. 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 the 7th clause 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 defines the minimum requirements for a well-managed organization.

In other words, noncompliance to an ISO 9001 requirement puts at risk an organization's ability to consistently and efficiently satisfy the expectations of its customers/ stakeholders.

b. **The six QMS requirements or "The Six Quality Procedures":** These procedures or requirements, as one may choose to call them, actually refer to sub-clause 4.1 (General requirements) under clause 4 (Quality Management System) of ISO 9001.

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):

i) Determine the processes needed for the QMS, and their application throughout the organization;

ii) Determine the sequence of the processes and their interactions;

iii) Determine the criteria and methods for operating and controlling the processes;

iv) Determine and ensure the availability needed resources and supporting information;

v) Check, measure and analyze the processes, where applicable; and

vi) Implement actions to achieve planned results and continual improvement of the processes. The processes needed for the QMS invariably include the processes for management activities (clause 5), provision of resources (clause 6), product realization (clause 7), and measurement, analysis, and improvement (clause 8).

Philosophically, ISO 9001 is formulated on the basis of management by objectives (MBOs) and draws upon eight quality management principles. Ideally therefore, quality assurance (QA) or total quality management (TQM) 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 TQM or quality assurance management (QAM) is the "Shewhart cycle"**,** also called "PDCA approach", meaning, "Plan-Do-Check-Act" [21, 22]. The foregoing is illustrated in **Figure 1** using NIPRD QMS processes as an example.

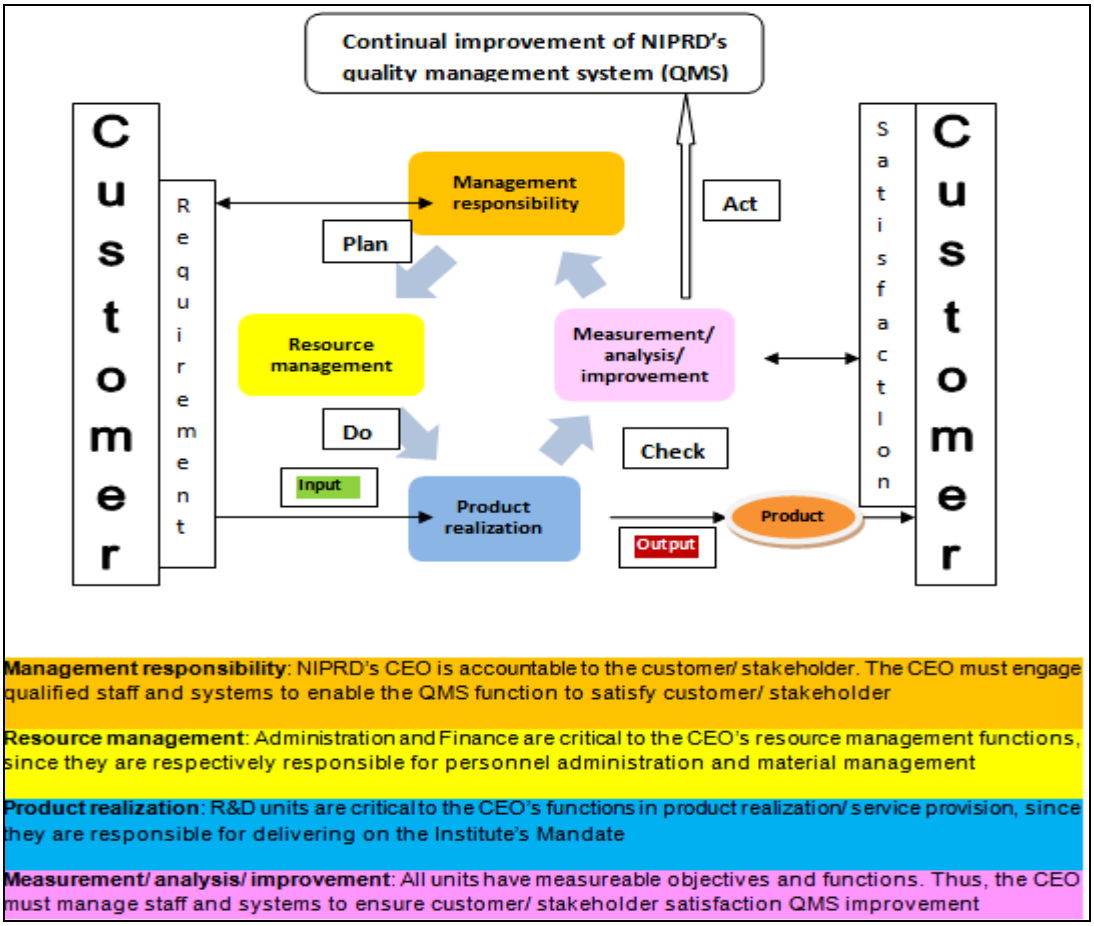

FIGURE 1: MANAGEMENT RESPONSIBILITY CORRESPONDS TO CLAUSE 5 OF ISO 9001; WHILE RESOURCE MANAGEMENT, PRODUCT REALIZATION AND MEASUREMENT/ ANALYSIS/ IMPROVEMENT CORRESPOND TO CLAUSES 6, 7 AND 8 RESPECTIVELY

Footnote to Figure 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.

Management responsibility: NIPRD's CEO is accountable to the customer/ stakeholder. The CEO must engage qualified staff and systems to enable the QMS function to satisfy customer/ stakeholder

Resource management: Administration and Finance are critical to the CEO's resource management functions, since they are respectively responsible for personnel administration and material management

Product realization: R&D units are critical to the CEO's functions in product realization/ service provision, since they are responsible for delivering on the Institute's Mandate

Measurement/ analysis/ improvement: All units have measureable objectives and functions. Thus, the CEO must manage staff and systems to ensure customer/ stakeholder satisfaction QMS improvement

3. **The eight quality management principles that underlie ISO 9001:** All ISO standards including ISO 9004 - *Managing for Sustained Success* and ISO 9001are formulated on the bases of 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.

4. Key terminologies of ISO 9001:2008

A. 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.

B. **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. Product realization is the subject of 7th clause of ISO 9001 and the main issue in this article as will be seen in the Results and Discussion.

C. 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.

D. **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 non-conformances (problems involving suppliers, customers, or internal problems).

E. **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.

F. 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 – basis for "Customer focus".

RESULTS AND DISCUSSION: Once the CEO (or the officer concerned in the herbal drug organization) is convinced of the merit of developing an herbal product from a named part of a named plant, a formal ethnobotanical survey is conducted, if necessary, to ascertain/ conduct the following scenarios/ attendant actions:

i. Where no toxicological data exist, evidence is sought to confirm that the use of the drug for least 20-30 years were without untoward effects.

ii. Where some toxicological data exist, evidence is sought to confirm that the period during which the drug had been in use is at least 20 years; that the health disorder treated with the drug justified the attendant risks; and that the number of patients so treated was of sufficient statistical power.

iii. Where there is a well-defined toxicity, attempts are made to establish its dose-dependency and to explain any possible consequence thereto.

iv. Where there is a potential for abuse, an appropriate approach to dealing with it must be articulated.

v. Where the period of use is less than 20 years, attempts are made to conduct a formal toxicity studies.

The scenarios/action above are as per WHO[7] as summarized in **Table 3**. In the meantime quality control studies designed as per WHO [6] are undertaken to confirm or verify the following, as described below:

Since, the regulatory requirements for an herbal product need not be less stringent than those for regular pharmaceuticals; its production should conform to good manufacturing practice (GMP) and relevant industrial standards, where such exist. Such conformities must take into cognizance the inherent variability of biological materials.

Accordingly, the following quality control actions described earlier [8, 9] should be considered:

i. Limits must be set for the starting materials.

ii. The manufacturing process must be chosen, such that mechanical efficiency and biochemical compatibility are simultaneously attained.

iii. The manufacturing process must be observable and reproducible.

iv. The finished product must pass relevant tests, including, where possible, one directly related to the disease condition of interest.

To attend to these steps methodically [8, 9], as set out and described in detail in **Tables 4-11**, is to develop a system for assuring the quality of herbal products that are in compliance with both WHO and ISO 9001 requirements. The contents of the Tables are briefly described as follows:

i. **Tables 4 and 5** deal with functions concerned with planning of product realization and customer-related processes.

ii. **Tables 6 and 7** deal with design and development processes.

iii. **Table 8** deals with purchasing processes.

iv. **Tables 9 and 10** deal with production and service provision.

v. **Table 11** deals with control of measuring and monitoring equipment.

While the successful application of the WHO model by NIPRD [21-23], had led to the development of Niprisan® - an antisickling phytomedicine, the application of ISO 9001 is widely applauded as the most successful industrial standard in world economic history [24-26].

TABLE 4: DEPARTMENTAL ROLES IN PLANNING OF PRODUCT REALIZATION AS PER ISO 9001:2008

Departmental roles + ISO 9001 requirements under Sub-clause 7.1: Planning of Product Realization	Salient points, directing principles and the main roles of departments in relation to the application of the QMS requirements for planning of product realization
Departments concerned Medicinal Plants Research & TM (MPRTM) ; Pharmacology & Toxicology (P&T); Microbiology, Virology & Biotechnology (MVBT); Medicinal Chemistry & Quality control (MCQC); and Pharmaceutical Technology & Raw Material Development (PTRMD) Recap of ISO 9001 requirements 1. Plan and develop the processes needed for product realization. 2. Keep the planning consistent with other requirements of the QMS and document it in a suitable form for organization. 4. Determine through the planning, as appropriate, the: a) Quality objectives and product requirements. b) Need for processes, documents, and resources. c) Verification, validation, monitoring, measurement, inspection, and test activities. d) Criteria for product acceptance. e) Records needed as evidence that the processes and resulting product meet requirements	Based on inputs from the departments, the CEO approves a material (eg: aerial parts *Mitracarpus scaber*) for development as dermal antifungal (coded: AF1). Input may be an MPRTM report that the material has been in use for skin conditions since antiquity. The CEO may require further inputs (eg: MVBT report that the material is antifungal). Once the CEO approves the material for AF1, a team led by a senior scientist (eg: a professor) is appointed, with a member or more from relevant departments. The Team Leader (TL) directs the research and reports to the CEO, with copies to all Heads of Department (HODs). Either the HOD or a representative on the team coordinates aspects of the study related to that department. The TL may for example direct as follows: 1. MPRTM: Confirm the name of the plant and determine how best to procure or cultivate/ collect the need parts; determine if similar materials have the same or similar prospects; and suggest or determine a processing procedure based on knowledge gathered from ethnobotanical survey. 2. P&T: Determine the effect of application of the material to the skin of healthy and fungal infected animals; determine the toxicity profile of the material; and suggest suitable doses for further animal (or possibly human) studies. 3. MVBT: Determine or confirm any antifungal effect of the material; determine the minimum inhibitory concentration of materials prepared as suggested by MPRTM or P&T; and suggest a line of action based on the results obtained. 4. MCQC: Determine the key physicochemical features of the material and establish parameters (eg: loss on drying, extractive matter, chromatographic fingerprints and marker substance) essential for identification and C-M-C. 5. PTRMD: Determine and establish a suitable formulation based on confirmed findings and legal/ customer requirements for the prospective product.

Footnote to Table 4: A document specifying the processes of the QMS (including the product realization processes), and the resources to be applied to a specific product, project or contract, can be referred to as a quality plan. The requirements in sub-clause 7.3 (Design and Development) can also be applied to the development of product realization processes.

TABLE 5: DEPARTMENTAL ROLES IN CUSTOMER-RELATED PROCESSES AS PER ISO 9001: 2008

Departmental roles + the 3 ISO 9001 requirements under Sub-clause 7.2: Customer-Related Processes	**Salient points, directing principles and the main roles of departments in relation to the application of the QMS requirements for customer related processes**
Departments concerned Medicinal Plants Research & TM (MPRTM) ; Pharmacology & Toxicology (P&T); Microbiology, Virology & Biotechnology (MVBT); Medicinal Chemistry & Quality control (MCQC); and Pharmaceutical Technology & Raw Material Development (PTRMD) **Recap of ISO 9001 requirements** **1. Requirements related to the product** Determine customer requirements: 1. Specified for the product (including delivery and post-delivery activities). 2. Not specified for the product (but needed for specified or intended use, where known). 3. Statutory and regulatory requirements applicable to the product. 4. Any additional requirements considered necessary by NIPRD. **2. Review of the requirements related to product the** Review the product requirements before committing to supply the product to the customer in order to: 1. Ensure product requirements are defined. 2. Resolve any requirements differing from those previously expressed. 3. Ensure its ability to meet the requirements. 4. Maintain the results of the review, and any subsequent follow-up actions. 5. When the requirements are not documented, they must be confirmed before acceptance. 6. If product requirements are changed, ensure relevant documents are amended and relevant personnel are made aware of the changed requirements. **3. Customer Communication** Determine and implement effective arrangements for communicating with customers on: 1. Product information. 2. Inquiries, contracts, or order handling (including amendments). 3. Customer feedback (including customer complaints).	If the TL's report to the CEO supports further action on AF1, the CEO directs TL to proceed with customer-related processes as per sub-clause 7.2. The TL may or may not reconstitute his team depending upon what is at stake. For example once it is decided that AF1 should be developed as an ointment, cream or lotion MPRTM, MCQC and PTRMD will feature prominently in the tasks ahead. For example MPRTM, MCQC and PTRMD need to concentrate on how best to provide AF1 in a suitable form efficiently and economically. The final design of the product rests on PTRMD in liaison with MCQC, which needs to develop procedures for qualifying the starting materials of AF1 and the finished product. If antifungal assay of AF1 is a requirement for the finished product, the necessary procedure needs to be developed by MVBT. Once PTRMD succeeds in producing trial sample of AF1, the CEO may direct that a clinical trial be conducted. The AF1 team may or may not be reconstituted, but the new direction of the research may call for a wider range of expertise from all departments/ units or even from outside.

Footnote to Table 5: Post-delivery activities include actions such as the need to institute a pharmacovigilance programme and the need to respond to reports of adverse effects. In situations where a formal review is not practical for each order, relevant product information such as catalogues or advertising material may be used as a basis for a review.

TABLE 6: DEPARTMENTAL ROLES IN DESIGN AND DEVELOPMENT PROCESSES AS PER ISO 9001: 2008

Departmental roles + 3 of the 7 ISO 9001 requirements under Sub-clause 7.3: Design and Development Processes	**Salient points, directing principles and the main roles of departments in relation to the application of the QMS requirements for design and development**
Departments concerned Medicinal Plants Research & TM (MPRTM) ; Pharmacology & Toxicology (P&T); Microbiology, Virology & Biotechnology (MVBT); Medicinal Chemistry & Quality control (MCQC); and Pharmaceutical Technology & Raw Material Development (PTRMD) **Recap of ISO 9001 requirements** **1. Design and development planning** Plan and control the product design and development such that the plan determines the: 1. Stages of design/ development. 2. Appropriate review, verification, and validation activities for each stage. 3. Responsibility and authority for design/ development. 4. Interfaces between the different groups involved must be managed to ensure effective communication/ clear assignment of responsibility. 5. Update, as appropriate, the planning output during design and development. **2. Design and development inputs** 1. Determine product requirement inputs and maintain records. 2. The inputs must include: a) Functional and performance requirements. b) Applicable legal requirements. c) Applicable information derived from similar designs. d) Requirements essential for design and development. 3. Review these inputs for adequacy. 4. Resolve any incomplete, ambiguous, or conflicting requirements. **3. Design and development outputs** 1. Document the outputs of the design and development process in a form suitable for verification against the inputs to the process. 2. The outputs must: a) Meet design and development input requirements. b) Provide information for purchasing, production, and service. c) Contain or reference product acceptance criteria. d) Define essential characteristics for safe and proper use. e) Be approved before their release.	Design and development can involve any department/ unit depending on what is at stake. Example: once the decision is taken to continue with the development of AM1, the following scenarios may unfold or ensue: 1. PTRMD strives to produce the most customer friendly and legally acceptable dosage form.. 2. MCQC strives to provide the most efficient and economic procedures for qualifying the raw material and the finished product. 3. P&T strives to provide facilities for animal studies and discover the most suitable study model. 4. MVBT strives to provide efficient antiplasmodial assay and any other microbiological tests required. 5. The onus of writing up the AM1 dossier for purposes of registration with a regulatory agency rests PTRMD, with assistance from departments/ units like MCQC, MVBT and ABCL. 6. Study design for clinical trials rests with the Office of the CEO, who may choose to utilize expertise from in NIPRD or outside.

Footnote to Table 6: Design and development review, verification, and validation have distinct purposes. They can be conducted and recorded separately or in any combination. Information for production and service can include details for product preservation.

TABLE 7: DEPARTMENTAL ROLES IN DESIGN AND DEVELOPMENT PROCESSES AS PER ISO 9001: 2008

Departmental roles + 4 of the 7 ISO 9001 requirements under Sub-clause 7.3: Design and Development Processes	**Salient points, directing principles and the main roles of departments in relation to the application of the QMS requirements for design and development**
Departments concerned Medicinal Plants Research & TM (MPRTM); Pharmacology & Toxicology (P&T); Microbiology, Virology & Biotechnology (MVBT); Medicinal Chemistry & Quality control (MCQC); and Pharmaceutical Technology & Raw Material Development (PTRMD) **Recap of ISO 9001 requirements** **4. Design and development review** 1. Perform reviews of design and development at suitable stages in accordance with planned arrangements, so as to: a) Evaluate the ability of the results to meet requirements. b) Identify problems and propose actions. 2. Ensure the reviews include representatives of the functions concerned. 3. Maintain results of reviews and subsequent follow-up. **5. Design and development verification** 1. Perform design and development verification in accordance with planned arrangements (Design and development planning) to ensure the output meets the design and development input requirements. 2. Maintain the results of the verification and subsequent follow-up actions. **6. Design and development validation** 1. Perform validation in accordance with planned arrangements (Design and development planning) to confirm the resulting product is capable of meeting the requirements for its specified application or intended use, where known. 2. When practical, complete the validation before delivery or implementation of the product. 3. Maintain the results of the validation and subsequent follow-up actions **7. Control of design and development changes** 1. Identify design and development changes and maintain records. 2. Review, verify, and validate (as appropriate) the changes and approve them before implementation. 3. Evaluate the changes in terms of their effect on constituent parts and products already delivered. 4. Maintain the results of the change review and subsequent follow-up actions.	Reviews of design and development are essential to discover the most economic/ efficient procedure in the departments/ units concerned with design and development. PTRMD, being the finishing department would particularly strive to produce the most customer friendly and legally acceptable dosage form. MCQC would strive to provide the most economic and efficient procedures for qualifying the raw material and the finished product. MVBT would similarly strive to provide the most economic and efficient antiplasmodial assay and any other microbiological tests required in AM1 raw material and finished product. It is essential that every department/ unit verifies the output of design and development against input in order to ensure that the fulfilment of the objective of the design. Designs need to be validated in order to confirm that product will perform as planned. When products or processes or service fail to perform as planned they must be re-designed, verified and validated

Footnote to Table 7: Information for production and service can include details for product preservation.

TABLE 8: DEPARTMENTAL ROLES IN PURCHASING PROCESSES AS PER ISO 9001: 2008

Departmental roles + the 3 ISO 9001 requirements under Sub-clause 7.4: Purchasing	**Salient points, directing principles and the main roles of departments in relation to the application of the QMS requirements for purchasing**
Departments concerned Medicinal Plants Research & TM (MPRTM) ; Pharmacology & Toxicology (P&T); Microbiology, Virology & Biotechnology (MVBT); Medicinal Chemistry & Quality control (MCQC); and Pharmaceutical Technology & Raw Material Development (PTRMD) **Recap of ISO 9001 requirements** **1. Purchasing process** 1. Ensure that purchased product conforms to its specified purchase requirements, noting that 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 product in accordance with the requirements. 3. Establish the criteria for selection, evaluation, and re-evaluation. 4. Maintain the results of the evaluations and subsequent follow-up actions. **2. Purchasing information requirements** 1. Ensure the purchasing information contains information describing the product to be purchased, including the requirements for: a) Approval of product, procedures, processes, and equipment. b) Qualification of personnel. 2. Include QMS requirements in the purchasing information – ie: define and sequence the requirements. 3. Ensure the adequacy of the specified requirements before communicating the information to the supplier. **3. Verification of purchased product** 1. Establish and implement the inspection or other necessary activities for ensuring the purchased products meet the specified purchase requirements. 2. If the organization or its customer proposes to verify the product at the supplier's location, state the intended verification arrangements and method of product release in the purchasing information.	Even though there is a central purchasing unit in NIPRD's Administration & Supplies Department concerned with general and special purchases, the criteria for the latter in product realization are furnished by the R&D departments/units concerned. For example in the development of AM1 the following procurement/ purchase scenarios apply: MPRTM would source or provide the criteria for the purchase of starting materials (including the root of *N. latifolia*) and other goods including reagents and equipment and accessories. P&T would source or provide criteria for all items (including animals and their feeds) required in toxicity, efficacy and other pharmacological studies. MVBT would source or provide criteria for all items (including microbial test organisms) and other goods like reagents and equipment. MCQC and PTRMD that must work hand in hand to develop the AM1 dosage form must source all the needed goods including analytical and manufacturing devices. The ABCL and NRC will similarly provide the criteria for all their requirements. Departments/ units are responsible for verifying purchased items supplied to them.

Footnote to Table 8: In view of the technical nature of some purchases it is necessary that the Purchasing Officer be familiar (or be specially assisted) with the technicalities involved and reasons behind a given purchase decision.

TABLE 9: DEPARTMENTAL ROLES IN PRODUCTION AND SERVICE PROVISION AS PER ISO 9001: 2008

Departmental roles + 2 of the 5 ISO 9001 requirements under Sub-clause 7.5: Production and Service Provision	**Salient points, directing principles and main roles of the departments in relation to the application of the QMS requirements for production and service provision**
Departments concerned with Medicinal Plants Research & TM (MPRTM) ; Pharmacology & Toxicology (P&T); Microbiology, Virology & Biotechnology (MVBT); Medicinal Chemistry & Quality control (MCQC); and Pharmaceutical Technology & Raw Material Development (PTRMD) **Recap of ISO 9001 requirements in respect of production and service provision processes** **1. Control of production and service provision** The planning and implementation production and service provision are conducted under controlled conditions to include, as applicable: availability of product characteristics information; availability of work instructions; use of suitable equipment; availability and use of monitoring and measuring equipment; implementation of monitoring and measurement activities; and implementation of product release, delivery, and post-delivery activities **2. Validation of processes for production and service provision** Wherever subsequent monitoring or measurement a product or service cannot verified, the processes involved should be validated before release of the product or provision of service. Such validation includes processes where deficiencies may become apparent only after product use or service delivery. The ability of processes to achieve the planned results should also be validated. Furthermore, the established validation arrangements should include, as applicable: criteria for process review and approval; approval of equipment; qualification of personnel; use of defined methods and procedures; requirements for records; and re-validation	As far as the actual production of herbal drug dosage form is concerned PTRMD is the last bus top. As for service provision, each departments can offer at least one or specialties. For example: MPRTM can provide herbalists with taxonomic data; P&T can provide herbalists with toxicity or efficacy data; MVBT can provide data on the comparative effect of an herb on difference cell species or the antiviral or antimicrobial potential of an herb; MCQC can furnish data essential for chemistry-manufacturing-control and posology; and PTRMD can provide the recipe for producing the approved dosage form, and write up the dossier for registering the product with a regulatory agency. It must be stated that any function not directly captured by any of the 5 departments is assumed by the Office of the CEO, who may delegate such functions within the organization or contract them out. Examples of jobs that may be so handled include highly specialized services, including clinical trials

Footnote to Table 9: Some pharmacopoeial or compendial tests such disintegration and dissolution tests for tablets and capsules may be applied to herbal preparations.

TABLE 10: DEPARTMENTAL ROLES IN PRODUCTION AND SERVICE PROVISION AS PER ISO 9001: 2008

Departmental roles + 3 of the 5 ISO 9001 requirements under Sub-clause 7.5: Identification and Traceability; Customer property; and Preservation of product	**Salient points, directing principles and main roles of R&D depts./ units in relation to the application of the QMS requirements for production and service provision**
Departments concerned with Medicinal Plants Research & TM (MPRTM) ; Pharmacology & Toxicology (P&T); Microbiology, Virology & Biotechnology (MVBT); Medicinal Chemistry & Quality control (MCQC); and Pharmaceutical Technology & Raw Material Development (PTRMD) **Recap of ISO 9001 requirements** **3. Identification and Traceability** 1. Identify, where appropriate, the product by suitable means during product realization. 2. Identify the product status with respect to monitoring and measurement requirements throughout product realization. 3. Where traceability is a requirement, control the unique identification of the product and maintain records. **4. Customer Property** 1. Exercise care with any customer property while it is under the control of, or being used by, NIPRD. 2. Identify, verify, protect, and safeguard customer property provided for use, or for incorporation into the product. Record and report any lost, damaged, or unsuitable property to the customer. **5. Preservation of product** Preserve the product during internal processing and delivery to the intended destination in order to maintain conformity to requirements. As applicable, preservation includes: 1) identification, 2) handling, 3) packaging, 4) storage, and 5) protection	One of the key objectives of C-M-C is to propose or help to establish a probable route of production to be carried on pilot scale by PTRMD. As in the production of chemical medicines various in-process quality control procedures are required. These require that MCQC and/or PTRMD must be able 1) identify, where appropriate, the product by suitable means during product realization; and 2) identify the product status with respect to monitoring and measurement requirements throughout product realization. MCQC and/ or PTRMD need to have the following where necessary and feasible: a) a defined reference active crude extract (RACE), b) a defined marker substance (DMS) and TLC, HPLC or GC-MS fingerprints of RACE and DMS. These strategies are essential for product realization and for regulatory purposes – they are the instruments by which problems can be traced to their sources, hence the basis of traceability. Obviously, PTRMD or any department must exercise care with any customer property under their control. They must record and promptly report any loss or damage to the customer. This approach is essential for fiscal accountability and for addressing specific regulatory concerns associated with some pharmacologic agents like narcotics and poisons.

Footnote to Table 10: Chromatographic fingerprints and the use of marker substance and the availability of reference crude extracts are essential as a means by which identification and traceability can be maintained in herbal drug production. Customer property can include the personal data and traditional knowledge revealed by an herbalist.

TABLE 11: DEPARTMENTAL ROLES IN CONTROL OF M&M EQUIPMENT AS PER ISO 9001: 2008

Departmental roles + 3 of the 5 ISO 9001 requirements under Sub-clause 7.6: The equipment most in need of calibration and re-calibration include: gravimetric instruments, volumetric wares, photometers, refractometers, and other electrochemical devices	**Salient points, directing principles and main roles of departments in relation to the application of the QMS requirements for control of measuring and monitoring equipment**
Departments concerned with Medicinal Plants Research & TM (MPRTM) ; Pharmacology & Toxicology (P&T); Microbiology, Virology & Biotechnology (MVBT); Medicinal Chemistry & Quality control (MCQC); and Pharmaceutical Technology & Raw Material Development (PTRMD) **Recap of ISO 9001 requirements** **Control of Measuring and Monitoring Equipment** 1. Determine the monitoring and measurements to be made, and the required equipment, to provide evidence of product conformity. 2. Use and control the monitoring and measuring devices to ensure that measurement capability is consistent with monitoring and measurement requirements. Where necessary to ensure valid results: a) Calibrate and/or verify the measuring equipment at specified intervals or prior to use. b) Calibrate the equipment to national or international standards (or record other basis). c) Adjust or re-adjust as necessary. d) Identify the measuring equipment in order to determine its calibration status. e) Safeguard them from improper adjustments. f) Protect them from damage and deterioration 3. Assess and record the validity of prior results if the device is found to not conform to requirements. 4. Maintain records of the calibration and verification results. 5. Confirm the ability of software used for monitoring and measuring for the intended application before its initial use (and reconfirmed as necessary).	Standard practice requires all R&D departments/ units to calibrate their equipment as may be prescribed by operating procedures or other official compendia. In doing so, among other control measures, they need to: 1) assess and record the validity of prior results if the equipment/ method are found not to conform to requirements; 2) maintain records of the results of calibration and verification; and 3) confirm or re-confirm the ability of any software or programme used for monitoring or measurement before its initial use. To ensure the validity of results, R&D departments/ units would normally: 1. Calibrate and/or verify the measuring equipment at specified intervals or prior to use. 2. Calibrate the equipment to national or international standards (or record other appropriate basis). 3. Adjust or re-adjust as necessary. 4. Identify the measuring equipment in order to determine its calibration status 5. Safeguard equipment from improper adjustments. Protect equipment from damage and deterioration

Footnote to Table 11: Some calibrations are done daily, some whenever the equipment is to be used, some seasonally and some yearly. The frequency of calibration is normally stated in the relevant SOPs or compendia or equipment SOP or manual.

CONCLUSION: Both ISO 9001's provisions for product realization and WHO guidelines for quality control and development of herbal drugs from Traditional Medicine can be applied to the research, development and actual production quality herbal medicines. We affirm that a widespread application of these guidelines will revolutionize herbalism worldwide and contribute immensely to the economy of countries that have a rich biodiversity and herbal tradition.

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