



## PRODUCT REALIZATION AND SERVICE PROVISION IN HERBAL DRUG RESEARCH AND DEVELOPMENT ACCORDING TO ISO 9001

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### ABSTRACT

Background: Product realization according to the International Organization for Standardization (ISO) includes: planning of product realization; customer-related processes; design and development; purchasing; production and service provision; and control of measuring and monitoring equipment, as specified in the 7<sup>th</sup> clause of ISO 9001.

Purpose: The article takes a critical look at product realization as per ISO 9001 and the critical stages of herbal drug research and development (R&D) from traditional medicine (TM), with a view to synthesizing a framework that can be used to introduce quality into herbal products from the stage of ethnobotanical survey, through product conception and development, up to the stage of clinical trials.

Methodology: The provisions of the 7<sup>th</sup> clause of ISO 9001 and the WHO model of herbal drug R&D as adopted by the Nigerian National Institute for Pharmaceutical Research and Development (NIPRD) were determinatively reviewed and fused to yield a framework which is then discussed in the context of guiding herbal drug R&D from TM.

Results and Discussion: The resulting tabular framework is discussed in terms of the applicability of the provisions of the 7<sup>th</sup> clause of ISO 9001 to the critical stages of herbal drug R&D at NIPRD, with the aim of introducing quality into herbal drug products.

Conclusion: The provisions of ISO 9001's 7<sup>th</sup> clause can be applied, albeit selectively, in introducing quality to herbal drug products developed from traditional herbal medicine.

**KEYWORDS:** International Organization for Standardization (ISO), Quality management system (QMS), Product realization, Herbal Drug, Research and Development (R&D)

### INTRODUCTION

#### The Rising Profile of Phytotherapy and the Need for Standardization

Earlier studies<sup>1,2</sup> established that Africa and Asia, especially China and India, have for long been the bastion of phytotherapy – the main subject of TM; that 1978 was the turning point in the current global popularity of phytotherapy following WHO's declaration of support; that the US Dietary Supplements Health Education Act (DSHEA)<sup>3</sup> of 1994 greatly promoted herbalism in America, albeit indirectly, through the innovative provision it made for user information<sup>4,5</sup>; and that a similar situation as in the US obtained in Europe, where the net effect of the European Directive on Traditional Herbal Medicinal Products (EDTHMP)<sup>6</sup> of 2004 had been to promote their production and use<sup>7</sup>. In terms of economics, the following fact is notable: Although, Asia contributed only US\$ 7.3 billion to herbal world trade in 1999<sup>8</sup>, by 2005, a mere 6 years later, China's contribution alone rose to US\$ 14 billion<sup>9</sup>. This stupendous growth was due to policies and programmes that favoured herbal medicine. Similar situations as in China held sway in Japan, South Korea and the Indian sub-continent, where government policies also favoured herbal medicine. The rising interest in phytotherapy is well exemplified by the data<sup>10</sup> in Figure 1. It thus seems to us that this growing interest and trade in herbal drugs call for higher quality and better regulation, which in turn call for standardization as proposed in ISO 9001.

### METHODOLOGY

The methodology consists of a determinative review of the 7<sup>th</sup> clause of ISO 9001 and NIPRD's *modus operandi* to generate a conceptual framework which is used as the basis

for applying the provisions of the clause to herbal drug research and development (R&D). The provisions of the clause (summarized in Tables 1-8) are fully described in ISO 9001:2008 obtainable from the International Organization for Standards, Basle, Switzerland, or from any of its national affiliates. However a synopsis of the five key clauses (4<sup>th</sup> - 8<sup>th</sup>) of ISO 9001:2008 and NIPRD's *modus operandi* are presently described.

#### A Synopsis on ISO 9001

ISO 9001:2008 is a minor modification of ISO 9001:2000 – the most anticipated industrial standard in history. The standard has five main categories of requirements/responsibilities, namely: 1) QMS requirements, embracing the general procedures and documentation requirements; 2) Management Responsibilities, that include commitment to quality management, customer focus, quality policy, quality planning, appointment of Quality Manager and the communication of that appointment to all interested parties, and conduct of periodic management reviews; 3) Resource Management, that include the provision of material resources, human resources, infrastructure and work environment; 4) Product Realization (also called: Process Management), that includes planning of product realization, customer-related processes, design and development, purchasing, production and service provision, and control of measuring and monitoring equipment; and 5) Measurement, Analysis and Improvement, that embrace all aspects of monitoring and measurement, control of nonconforming product, analysis of data, and improvement. The ISO 9001 QMS standard requires only six quality management procedures, and represents the accepted minimum requirements for a well managed organization. The standard is generic and does not

prescribe how to comply with its requirements. The QMS Process Model upon which the ISO 9001 is based<sup>11,12</sup> is illustrated in Figure 2, using NIPRD's core business of herbal drug R&D and the provision of related consultancy services as an example.

#### **NIPRD's Mandate in the Context of ISO 9001**

NIPRD's Mandate consists of research and development of health products including herbal drugs, biologicals, medical devices and allied products, including diagnostics, for the purpose of contributing to healthcare delivery in Nigeria and beyond. In furtherance of its desire to contribute more effectively to healthcare delivery, NIPRD decided in 2010 to formally adopt a QMS that will provide the framework it needs to monitor and improve its performance in any area it chooses. It chose the ISO 9001:2008 because of its suitability and popularity as the world's most established quality framework, being used by 1,064,000 organizations in 178 countries worldwide, as at 2011; and because the ISO 9000 series sets the standard not only in QMS, but management systems generally. ISO 9001:2008 is well known to have helped all kinds of organizations to succeed through improved customer/ stakeholder satisfaction, staff motivation and continual improvement. NIPRD's ongoing experimentation with ISO 9001:2008, which included courses on appreciation and auditing provided to a select staff of the Institute in November/ December 2011, revealed that the ISO 9000 series of standards consist of: ISO 9000 (Fundamentals and Vocabulary), which introduces the user to the concepts behind the management systems and specifies the terminology used; ISO 9001 (Requirements), which sets out the criteria needed to meet operations in accordance with the standard and gain certification; and ISO 9004 (Guidelines for performance improvement), which is based upon the eight quality management principles, designed to be used by top management as a framework to guide their organizations towards improved performance by considering the needs of all interested parties, not just customers/ stakeholders. On the whole, the progress of the experiment with ISO 9001:2008 in NIPRD has strengthened the conviction that the path to the Institute's ultimate effectiveness lies in adopting and holding fast to a management system that has proved its mettle worldwide.

#### **NIPRD's Organogram and Modus Operandi**

NIPRD's R&D organogram (Figure 2) consists of the Office of the Director General/ Chief Executive Officer – a senior biomedical scientist appointed by the President of Nigeria on the recommendation of the Minister of Health. Attached to the Office of the DG/ CEO are two key R&D units, namely: the Advanced Biology and Chemistry Laboratory (ABCL), headed by a senior scientist, who reports directly to the CEO and assists in key decisions like those linked with clinical trials; and the NIPRD Research Clinic (NRC), headed by a senior physician, who attends to community health issues and other duties assigned by the CEO including a role clinical trials. The Institute's core R&D activities are run by five technical departments, namely: Medicinal Plants Research & Traditional Medicine (MPRTM) – that researches plants used in traditional medicine, conducts ethnobotanical studies and recommends actions based on such studies; Pharmacology & Toxicology (P&T) – that screens materials for toxicity and efficacy and recommends actions, including follow up studies; Microbiology, Virology & Biotechnology (MVBT) – that screens materials against economic and non-economic

species and recommends actions, including further studies; Medicinal Chemistry & Quality Control (MCQC) – that standardizes materials to enable decisions on quality and quantity (ie: chemistry-manufacturing-control or C-M-C) issues to be taken, with a view to facilitating the production of clinical trial samples; and Pharmaceutical Technology & Raw Material Research & Development (PTRMD) – that produces clinical trial samples, participates in clinical trials and directs pilot production/ scale-up activities. Any of R&D departments can be assigned any duty the CEO considers relevant to NIPRD's Mandate. These include the provision of various industrial and health related consultancy services

#### **RESULTS AND DISCUSSION**

The conceptual framework generated from the determinative reviews is presented in Tables 1-8, corresponding to the 8 key sub-clauses of the 7<sup>th</sup> clause of ISO 9001:2008. Each Table gives a recap of the pertinent provisions of the clause and their relevance or applicability to herbal drug R&D as practised at NIPRD. Although the position of the DG/ CEO of NIPRD is a political appointment, the job requires him or her to be a technocrat/ biomedical scientist. He or she needs to be a technocrat to understand the socio-political undercurrent of high policy and the dynamics and economics of policy implementation. Incidentally, NIPRD was created in 1987 as one of several World Bank sponsored strategies to reduce Nigeria's overdependence on medical imports and to promote industrialization of indigenous medical knowledge and technologies. NIPRD's CEO needs to be a biomedical scientist in order to better appreciate the deeds and implications of Institute's Mandate, and to more accurately and circumspectly identify the needed resources, order of priorities and in order to more adroitly command their deployment of resources. The immediate technical lieutenants of the CEO include chemists and biomedical scientists drawn from various specialties as contained in the British<sup>13</sup> "Orange Guide". Table 1 addresses planning of product realization and shows how each R&D department/ unit may be involved. Developments proceeding from ethnobotanical survey invariably involve MPRTM. Similarly MCQC and PTRMD must be involved in C-M-C and in the development of viable dosage forms. P&T and MVBT must be involved if decisions on toxicity/ efficacy and effects of the herb on human cells as compared to pathogens are key the development process. Since success can only follow from proper planning of product realization, its execution must be thorough. Clinical studies, especially phased trials of allopathics, often appears at later stages of drug development, but for herbs used in TM, such studies called observational studies come quite early in the development process<sup>15,16</sup>. This means that plans for observational studies (which is within the purview of the CEO) may be conceived at this stage; or at stage of customer-related processes (Table 2), where P&T, NRC and PTRMD will play a key role; or at the stage of design and development processes (Tables 3 and 4), where the roles of MCQC and PTRMD are most critical. Since purchased items are critical to product realization and service provision (Tables 5-7), the onus is upon the HODs to ensure that correct items are purchased by providing their specifications and by inspecting such items before approving them; and by validating the processes utilizing those items. Biomedical R&D as a whole is highly dependent on a myriad of equipment – some very complex and costly, and most require frequent calibrations (Table 8). Great attention is paid

to calibrations for two main reasons: the practice is critical to all measurements and monitoring of biochemical and biophysical phenomena; and because such measurement/monitoring provides the means by which organizations can adjust their products and services, analyze performances and aim for continual improvement of the quality management system (QMS). Given the rapid growth of the Chinese and India economies in recent times, it notable that, in 2009, of the about 1 million ISO 9001 certified organizations in the world, about 39% were in China (~26%) and India (~13%) alone<sup>17</sup>. We imagine therefore, that applying ISO 9001 to herbal drug RD will not only lead to higher quality but will boost herbal drug trade and increase their utilization, with positive multiplier effects on the economy. Indeed, NIPRD chose the ISO 9001:2008 QMS based on the benefits of the standard. The global popularity of ISO 9001QMS is generally attributed to the fact that major purchasers require their suppliers to hold ISO 9001 certification<sup>17,18</sup>; studies indicate significant financial benefits for organizations certified to ISO 9001<sup>18,19</sup>; and similar superior operational performance of ISO certified firms has been severally confirmed<sup>20-23</sup>.

## CONCLUSION

ISO 9001 is an international standard designed to address systemic change (ie: a change that affects an organization as whole). The standard is popular because major purchasers require their suppliers to hold ISO 9001 certification and studies show significant financial benefits and superior operational performance for organizations certified to ISO 9001. Based on the foregoing we affirm that ISO 9001 can be applied to herbal drug research and development and by so doing, add quality to herbal products and improve their trade and utilization.

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**Table 1: Departmental roles in planning of product realization as per ISO 9001:2008**

Departments/ units concerned/ Recap of ISO 9001 requirements.	Salient points, directing principles and main roles of R&D depts./ units in relation to the application of the QMS requirements associated with planning of product realization as per sub-clause 7.1 of ISO 9001:2008
<p><b><u>NIPRD depts. / units concerned with R&amp;D</u></b></p> <p>1. CEO's Office. 2. MPRTM. 3. P&amp;T. 4. MVBT. 5. MCQC. 6. PTRMD. 7. ABCL. 8. NRC</p> <p><b><u>Recap of ISO 9001 requirements in planning of product realization</u></b></p> <p>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 NIPRD. 4. Determine through the planning, as appropriate, the:</p> <p>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</p>	<p>Based on inputs from departments/ units, the CEO approves a material (eg: root of <i>Nauclea latifolia</i>) for development as oral antimalarial (coded: AM1). Input may be an MPRTM report that the material has been in use for malarial since antiquity. The CEO may require further inputs (eg: MVBT report that the material is antiplasmodial). Once the CEO approves the material for AM1, a team led by a senior scientist (eg: a professor) is appointed, with a member or more from relevant departments/ units. 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:</p> <p>1. MPRTM: Confirm the names of the plant and determine how best to procure or cultivate/ collect the plant material; determine if similar materials have the same or similar prospects; and suggest or determine a processing procedure based on knowledge gathered from ethnobotanical survey.</p> <p>2. P&amp;T: Determine the effect of the material on animals infected with malaria and suggest possible modes of action; determine the toxicity profile of the material; and suggest suitable doses for further animal (or possibly human) studies.</p> <p>3. MVBT: Determine or confirm any antiplasmodial effect of the material; determine the minimum inhibitory concentration of materials prepared as suggested by MPRTM or P&amp;T; and suggest a line of action based on the results obtained.</p> <p>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.</p> <p>5. PTRMD: Determine and establish a suitable dosage form based on confirmed findings and legal/ customer requirements for the prospective product. PTRMD finalizes registration dossiers with assistance from other department especially MCQC as demonstrated elsewhere<sup>14</sup>.</p>

**Footnote to Table 1:** 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 2: Departmental roles in customer-related processes as per ISO 9001: 2008**

Departments/ units concerned/ Recap of ISO 9001 requirements. There are 3 QMS processes/ requirements under sub-clause 7.2 (Customer-related processes), namely: - Requirements related to the product; Review of the requirements related to the product; and Customer Communication	Salient points, directing principles and main roles of R&D depts./ units in relation to the application of the QMS requirements associated with planning of product realization as per sub-clause 7.2 of ISO 9001:2008
<p><b><u>NIPRD depts. / units concerned with R&amp;D</u></b></p> <p>1. CEO's Office. 2. MPRTM. 3. P&amp;T. 4. MVBT. 5. MCQC. 6. PTRMD. 7. ABCL. 8. NRC</p> <p><b><u>Recap of ISO 9001 requirements in respect of customer-related processes</u></b></p> <p><b>1. Requirements related to the product</b></p> <p>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.</p> <p><b>2. Review of the requirements above</b></p> <p>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.</p> <p><b>3. Customer Communication</b></p> <p>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).</p>	<p>If the report from the TL to the CEO supports further action on AM1, 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 AM1 should be developed as a powder, capsule or tablet MPRTM, MCQC and PTRMD will feature prominently in the tasks ahead. For example MPRTM, MCQC and PTRMD need to concentrate on how best to generate the AM1 dry powder 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 AM1 and the finished product. If antiplasmodial assay of AM1 is a requirement for the finished product, the necessary procedure needs to be developed by MVBT. Once PTRMD succeeds in producing trial sample of AM1, the CEO may direct that a clinical trial be conducted. The AM1 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 NIPRD. The CEO's access to the services of ABCL and NRC and to outside expertise is critical and strategic in clinical studies.</p>

**Footnote to Table 2:** 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 3: Departmental roles in design and development processes as per ISO 9001: 2008**

Departments/ units concerned/ Recap of ISO 9001 requirements. There are 7 QMS processes/ requirements under 7.3 (Design & Development) of which 3 are described in this Table, namely: - Design and development planning; Design and development inputs; and Design and development outputs	Salient points, directing principles and main roles of R&D depts./ units in relation to the application of the QMS requirements associated with design and development as per sub-clause 7.3 of ISO 9001:2008
<p><b>NIPRD depts. / units concerned with R&amp;D</b>  1. CEO's Office. 2. MPRTM. 3. P&amp;T. 4. MVBT. 5. MCQC. 6. PTRMD. 7. ABCL. 8. NRC</p> <p><b>Recap of ISO 9001 requirements in respect of design and development processes</b></p> <p><b>Design and Development</b></p> <p><b>1. Design and development planning</b>  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.</p> <p><b>2. Design and development inputs</b>  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.</p> <p><b>3. Design and development outputs</b>  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.</p>	<p>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:</p> <ol style="list-style-type: none"> <li>1. PTRMD strives to produce the most customer friendly and legally acceptable dosage form..</li> <li>2. MCQC strives to provide the most efficient and economic procedures for qualifying the raw material and the finished product.</li> <li>3. P&amp;T strives to provide facilities for animal studies and discover the most suitable study model.</li> <li>4. MVBT strives to provide efficient antiparasmodial assay and any other microbiological tests required.</li> <li>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.</li> <li>6. Study design for clinical trials rests with the Office of the CEO, who may choose to utilize expertise from in NIPRD or outside.</li> </ol>

**Footnote to Table 3:** 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 4: Departmental roles in design and development processes as per ISO 9001: 2008**

Departments/ units concerned/ Recap of ISO 9001 requirements. There are 7 QMS processes/ requirements under 7.3 (Design & Development), of which 4 are described in this Table, namely: - Design and development review; Design and development verification; Design and development validation; and Control of design and development changes	Salient points, directing principles and main roles of R&D depts./ units in relation to the application of the QMS requirements associated with design and development as per sub-clause 7.3 of ISO 9001:2008
<p><b>NIPRD depts. / units concerned with R&amp;D</b>  1. CEO's Office. 2. MPRTM. 3. P&amp;T. 4. MVBT. 5. MCQC. 6. PTRMD. 7. ABCL. 8. NRC</p> <p><b>Recap of ISO 9001 requirements in respect of design and development processes</b></p> <p><b>4. Design and development review</b>  1. Perform systematic reviews of design and development at suitable stages in accordance with planned arrangements (Design and development planning) to: a) Evaluate the ability of the results to meet requirements. b) Identify problems and propose any necessary actions. 2. The reviews must include representatives of the functions concerned with the stage being reviewed. 3. Maintain the results of reviews and subsequent follow-up actions.</p> <p><b>5. Design and development verification</b>  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.</p> <p><b>6. Design and development validation</b>  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</p> <p><b>7. Control of design and development changes</b>  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.</p>	<p>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.</p> <p>MCQC would strive to provide the most economic and efficient procedures for qualifying the raw material and the finished product.</p> <p>MVBT would similarly strive to provide the most economic and efficient antiparasmodial 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.</p> <p>When products or processes or service fail to perform as planned they must be re-designed, verified and validated</p>

**Footnote to Table 4:** Information for production and service can include details for product preservation.

**Table 5: Departmental roles in purchasing processes as per ISO 9001: 2008**

Departments/ units concerned/ Recap of ISO 9001 requirements. There are 3 QMS processes/ requirements under sub-clause 7.4 (Purchasing), namely: - Purchasing process; Information requirement; and Verification of purchased product	Salient points, directing principles and main roles of R&D depts./ units in relation to the application of the QMS requirements associated with design and development as per sub-clause 7.3 of ISO 9001:2008
<p><b><u>NIPRD depts. / units concerned with R&amp;D</u></b>  1. CEO's Office. 2. MPRTM. 3. P&amp;T. 4. MVBT. 5. MCQC. 6. PTRMD. 7. ABCL. 8. NRC</p> <p><b><u>Recap of ISO 9001 requirements in respect of purchasing processes</u></b>  <b>Purchasing</b>  <b>1. Purchasing process</b>  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.</p> <p><b>2. Purchasing information requirements</b>  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.</p> <p><b>3. Verification of purchased product</b>  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.</p>	<p>Even though there is a central purchasing unit in NIPRD's Administration &amp; Supplies Department concerned with general and special purchases, the criteria for the latter in product realization are furnished by the R&amp;D departments/units concerned. For example in the development of AM1 the following procurement/ purchase scenarios apply:</p> <p>MPRTM would source or provide the criteria for the purchase of starting materials (including the root of <i>N. latifolia</i>) and other goods including reagents and equipment and accessories. P&amp;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.</p>

**Footnote to Table 5:** 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 6: Departmental roles in production and service provision as per ISO 9001: 2008**

Departments/ units concerned/ Recap of ISO 9001 requirements. There are 5 QMS processes/ requirements under sub-clause 7.5 (Production and Service Provision), namely: - Control of production and service provision; Validation of processes for production and service provision; 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 associated with design and development as per sub-clause 7.3 of ISO 9001:2008
<p><b><u>NIPRD depts. / units concerned with R&amp;D</u></b>  1. CEO's Office. 2. MPRTM. 3. P&amp;T. 4. MVBT. 5. MCQC. 6. PTRMD. 7. ABCL. 8. NRC</p> <p><b><u>Recap of ISO 9001 requirements in respect of production and service provision processes</u></b>  <b>Production and Service Provision</b>  <b>1. Control of production and service provision</b>  Plan and carry out production and service provision under controlled conditions to include, as applicable: a) Availability of product characteristics information. b) Availability of work instructions, as necessary. c) Use of suitable equipment. d) Availability and use of monitoring and measuring equipment. e) Implementation of monitoring and measurement activities. f) Implementation of product release, delivery, and post-delivery activities</p> <p><b>2. Validation of processes for production and service provision</b>  1. Validate any production or service provision where subsequent monitoring or measurement cannot verify the output. Such validation includes processes where deficiencies may become apparent only after product use or service delivery. 2. Demonstrate through the validation the ability of processes to achieve the planned results. 3. Establish validation arrangements including, as applicable: a) Criteria for process review and approval. b) Approval of equipment. c) Qualification of personnel. d) Use of defined methods and procedures. e) Requirements for records. f) Re-validation</p>	<p>As far as the actual production of herbal drug products is concerned PTRMD is the last bus stop. But for service provision, each of the R&amp;D departments/ units of NIPRD has at least one or specialties. For example: MPRTM can provide herbalists with taxonomic data; P&amp;T can provide herbalists toxicity or efficacy data; MVBT can provide data on the comparative effect of an herb on economic and non-economic species or the antimicrobial potential of an herb; MCQC can furnish data essential for chemistry-manufacturing –control of an herbal medicine; and aside from developing a suitable dosage form for an herbal medicine, PTRMD can write up the dossier for registering and herbal medicine with a regulatory agency.</p> <p>In addition to the foregoing ABCL can provide such highly specialized services as forensic analysis and chemical synthesis. Aside from providing its immediate community with healthcare services, NRC is a key element in NIPRD's clinical research planning and strategy. MCQC, through its pharmacokinetic studies, provides government with bioequivalence data that essential in national drug policies. Just like pharmaceuticals, herbal medicine are required to pass a battery of tests such as identification and disintegration tests (tablets and capsules) before they approved.</p>

**Footnote to Table 6:** Some pharmacopeial or compendial tests such disintegration and dissolution tests for tablets and capsules may be applied to herbal preparations.

**Table 7: Departmental roles in production and service provision as per ISO 9001: 2008**

Departments/ units concerned/ Recap of ISO 9001 requirements. There are 5 QMS processes/ requirements under sub-clause 7.5 (Production and Service Provision), namely: - Control of production and service provision; Validation of processes for production and service provision; 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 associated with design and development as per sub-clause 7.3 of ISO 9001:2008
<p><b><u>NIPRD depts. / units concerned with R&amp;D</u></b></p> <p>1. CEO's Office. 2. MPRTM. 3. P&amp;T. 4. MVBT. 5. MCQC. 6. PTRMD. 7. ABCL. 8. NRC</p> <p><b><u>Recap of ISO 9001 requirements in respect of production and service provision processes</u></b></p> <p><b>3. Identification and Traceability</b></p> <p>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.</p> <p><b>4. Customer Property</b></p> <p>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.</p> <p><b>8. Preservation of product</b></p> <p>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</p>	<p>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.</p>

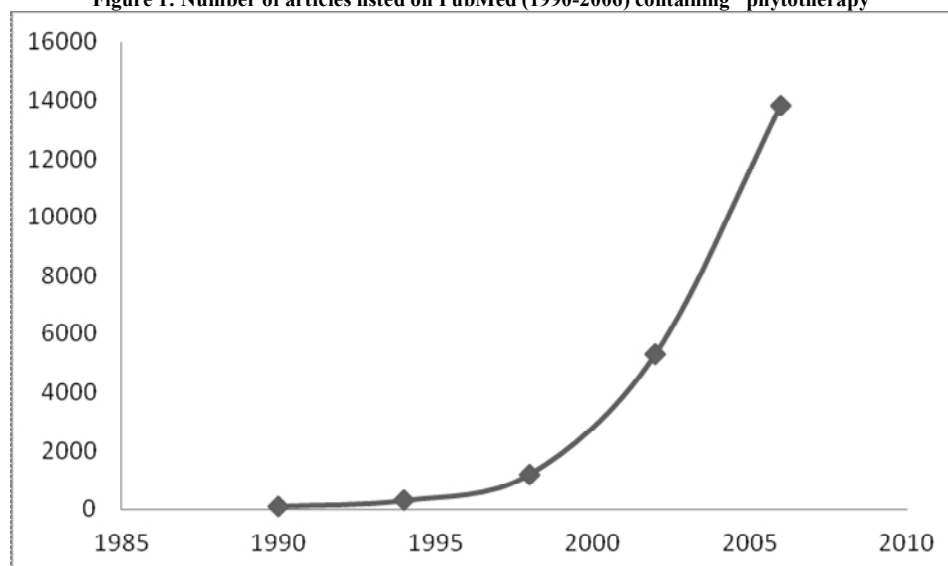
**Footnote to Table 7:** Chromatographic fingerprints and the use of marker substance and the availability of reference crude extracts are essential as a means by which identification and traceability can be maintained in herbal drug production. Customer property can include the personal data and traditional knowledge revealed by an herbalist.

**Table 8: Departmental roles in control of M&M equipment as per ISO 9001: 2008**

Departments/ units concerned/ Recap of ISO 9001 requirements. Some of the equipment most in need of calibration and re-calibration include: gravimetric instruments, volumetric wares, photometers, refractometers, electromeric equipment and other electronic devices	Salient points, directing principles and main roles of R&D depts./ units in relation to the application of the QMS requirements associated with design and development as per sub-clause 7.3 of ISO 9001:2008
<p><b><u>NIPRD depts. / units concerned with R&amp;D</u></b>  1. CEO's Office. 2. MPRTM. 3. P&amp;T. 4. MVBT. 5. MCQC. 6. PTRMD. 7. ABCL. 8. NRC</p> <p><b><u>Recap of ISO 9001 requirements in respect of control of measuring and monitoring (M&amp;M) equipment processes</u></b></p> <p><b><u>Control of Measuring and Monitoring Equipment</u></b></p> <ol style="list-style-type: none"> <li>Determine the monitoring and measurements to be made, and the required equipment, to provide evidence of product conformity.</li> <li>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: <ol style="list-style-type: none"> <li>Calibrate and/or verify the measuring equipment at specified intervals or prior to use.</li> <li>Calibrate the equipment to national or international standards (or record other basis).</li> <li>Adjust or re-adjust as necessary.</li> <li>Identify the measuring equipment in order to determine its calibration status.</li> <li>Safeguard them from improper adjustments.</li> <li>Protect them from damage and deterioration</li> </ol> </li> <li>Assess and record the validity of prior results if the device is found to not conform to requirements.</li> <li>Maintain records of the calibration and verification results.</li> <li>Confirm the ability of software used for monitoring and measuring for the intended application before its initial use (and reconfirmed as necessary).</li> </ol>	<p>Standard practice requires all R&amp;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&amp;D departments/ units would normally:</p> <ol style="list-style-type: none"> <li>Calibrate and/or verify the measuring equipment at specified intervals or prior to use.</li> <li>Calibrate the equipment to national or international standards (or record other appropriate basis).</li> <li>Adjust or re-adjust as necessary.</li> <li>Identify the measuring equipment in order to determine its calibration status</li> <li>Safeguard equipment from improper adjustments. Protect equipment from damage and deterioration</li> </ol>

**Footnote to Table 8:** 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.

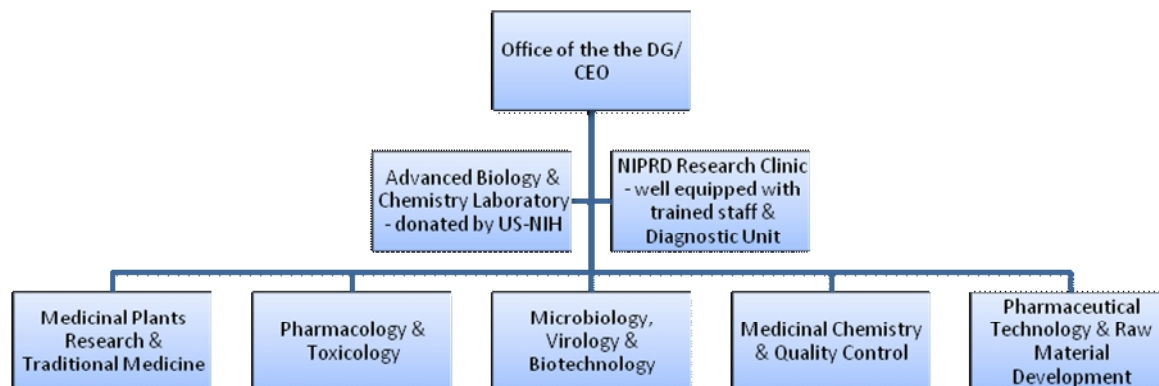
**Figure 1: Number of articles listed on PubMed (1990-2006) containing "phytotherapy"**



**Footnote to Figure 1:** Number of articles listed on PubMed (y-axis) from 1990-2006 (x-axis) containing the word "phytotherapy". Data derived from: Phytotherapy – Wikipedia (2007).

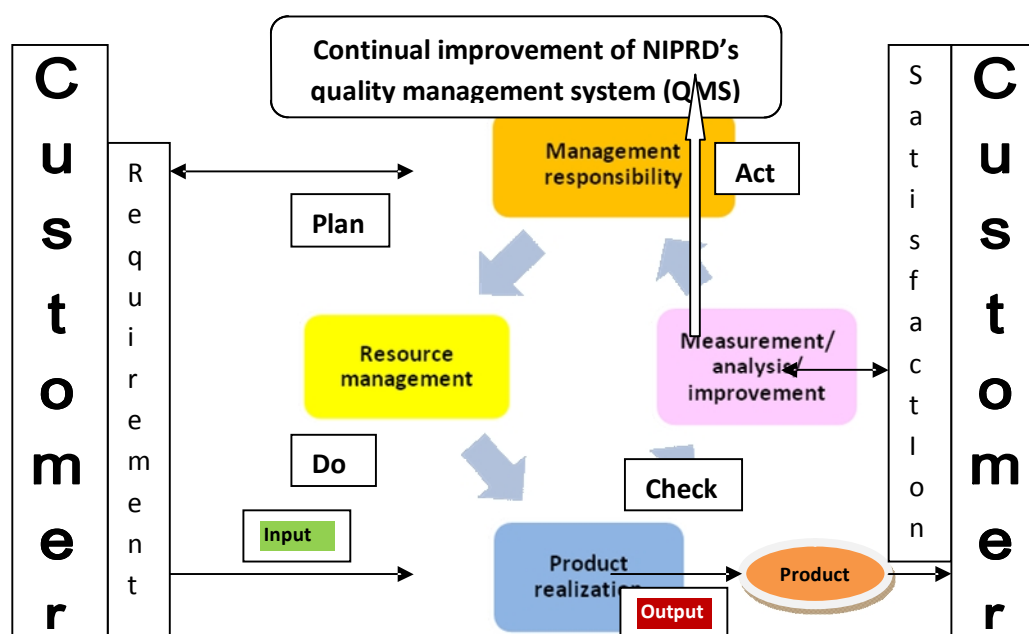


**Figure 2: NIPRD's research and development organogram**



**Footnote to Figure 2:** The departments/ units above are abbreviated as follows: Advanced Biology & Chemistry Laboratory (ABCL); NIPRD Research Clinic (NRC); Medicinal Plants Research and Traditional Medicine (MPRTM); Pharmacology & Toxicology (P&T); Microbiology, Virology and Biotechnology (MVBT); Medicinal Chemistry and Quality Control (MCQC); pharmaceutical Technology and Raw Material Development (PTRMD)

**Figure 3: NIPRD's core business in the context of Plan-Do-Check-Act Approach**



**Footnote to Figure 3:** Management responsibility corresponds to clause 5 of ISO 9001; while Resource management, Product

**Management responsibility:** NIPRD's CEO is accountable to the customer/ stakeholder. The onus is upon the CEO to engage the right calibre of personnel and system in every unit to enable the QMS function optimally so that the customer/ stakeholder can derive satisfaction.

**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, a major function of the CEO is to motivate and manage the various workers and systems to enable them satisfy the customer/ stakeholder and to improve the OMS on a continual basis