**UNIVERSITY OF NAIROBI**
**SCHOOL OF COMPUTINGAND INFORMATICS**

# Towards Data Architecture Integration for the Processes ofClinical Trials and Therapeutic Products Regulation at Kenya Pharmacy and Poisons Board.

**BY:**

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# DECLARATION

## DECLARATION BY THE CANDIDATE

I hereby declare that this project is my original work and has not been presented for a degree award in any other institution.

_____ _____

**Gedion Murimi Munyi** **Date**

## DECLARATION BY THE SUPERVISOR

This thesis has been submitted for examination with my approval as University Supervisor

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## DEDICATION

To my wife, Penina Njeri and my daughters Candice Kathomi and Jael Gakenia, thank you for your prayers.

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A

Active Pharmaceutical Ingredient (API)....58

C

Clinical Data Interchange Standards Consortium (CDISC) ....31
Clinical Trials Registry (CTR)....32
Common Technical Document (CTD)....36

D

Departement De La Pharmacie, Du Medicament Et Des Laboratoires (DPML) ....94
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## ABSTRACT

While therapeutic products have been with us for millennia, the question of how the quality, safety and efficacy of these products can be achieved and monitored effectivelystill eludes us. Many methods have been employed over time with varying degrees of success.

In the modern world the process of ensuring safety, quality and efficacy starts at drug development (molecule), testing (clinical trials), and registration by a competent authority (regulatory body) and finally post registration marketing surveillance. To do this data is gathered throughout the regulatory steps and used to determine the fitness of the product in its intended purpose. This is a process carried out by the regulator authority.

In Kenya the regulatory authority is Pharmacy and Poisons Board (Board). The Board regulates clinical trials and registration of therapeutic products in line with international standards. This is a process flaunted with challenges taking into account the law does not explicitly require the Board to regulate clinical trials and most clinical trials are done outside Kenya.

This report proposes how the Pharmacy and Poisons Board can utilize information technology to overcome regulatory challenges and achieve international standards, by integrating data from Clinical Trials Registry and Electronic Common Technical Document repositories. Using a mathematical formula proposed in this report, the Board can integrate data from clinical trials repository into the therapeutic products repository as specific data set areas that can be used to inform the product registration process as required by law. By using the formula to integrate the two repositories, the Board will meet international standards, overcome its regulatory challenges and still be in position to absorb any changes in international standards or local laws without having to change or re-engineer its systems.

Desk reviews of Pharmacy and Poisons Board guidelines, policies, existing laws and international standards were done together none structured interviews conducted in the East Africa National Medicines Registration Authorities. The results from the research show processes that are in need of re-engineering and laws and policies that need to be changed to allow for clinical trials to be made mandatory during therapeutic product evaluation.

The report concludes that there is need to depart from traditions in therapeutic products management and change the clinical trials and therapeutic products evaluation processes, tools and standardsto reflect a modern appreciation of the existence of information management technologies in data management.

# CHAPTER ONE – INTRODUCTION

## 1.0 Introduction

### *1.0.1 General Introduction*

A therapeutic product (drug) is a substance which may have medicinal, intoxicating, performance enhancing or other effects when taken or put into a human body or the body of another animal and is not considered a food or exclusively a food (Laws of Kenya, 2009).

Therapeutic products include complementary medicines such as most dietary supplements and herbal medicines; over-the-counter medicines and prescription medicines; medical devices such as contact lenses, condoms, hearing aids, heart valves, pace makers, endoscopes etc. Blood and blood products, and cellular and tissue therapies are also examples of therapeutic products. It is important to regulate pre-market and post-market safety, quality and efficacy of these products so that consumers are assured that their health and safety is safeguarded (Australia New Zealand Therapeutic Products Agency, 2007).

Medicines form a major part of an effective healthcare system. The main objective of such a healthcare system is to provide the public access to medicines that are of good quality, safety and efficacy and that are economically affordable. This is captured clearly in the Kenya National Drug Policy of 2006 and the mission statement of the Pharmacy and Poisons Board (Pharmacy and Poisons Board Kenya, 2007).

Medicines regulation involves the process of reviewing and assessing a therapeutic product dossier to support a medicinal product in view of its registration approval through marketing authorization also known as product license. This process is performed within a legislative framework which defines the requirements necessary for application to the Pharmacy and Poisons Board (Board), details on the assessment procedure (based on quality, efficacy and safety criteria) and the grounds for approval or rejection of the application, and also the circumstances where a marketing authorization already granted may be withdrawn, suspended or revoked.

Therapeutic product evaluation is done by reviewing paper documents (dossier) prepared using a format known as the Common Technical Document that defines what contents are required in the dossier and in which order and format. Laboratory analysis of drug samples is

done to verify that the chemical composition of the drug is consistent with the dossier. The Pharmacy and Poisons Board adopted the International Committee on Harmonisation (ICH) Electronic Common Technical Document(eCTD) format. The eCTD allows the applicants to submit the dossier electronically and the Pharmacy and Poisons Board reviewers to review the document electronically.

## 1.1 Statement of the Problem

### *1.1.1 General Statement of the Problem*

While there is no dispute on the importance and role of eCTD in the regulation of therapeutic products and the importance of the CTR in the management of clinical and non-clinical trials of new therapeutic products and post marketing authorization surveillance, the impact of the data contained in the two data architectures can't be fully appreciated. The reason for this is that the two data sets are gathered separately with references to each other. Though CTR is needed before a product can be registered, the CTR is only referenced in Module four of the eCTD and only very little data of the original CTR is used in the eCTD. This in turn denies the evaluators of eCTD dossiers the benefits of detailed research findings in their decision making. On the other hand CTR only references sections of the eCTD like module two and does not get very detailed information of the product being investigated. Actually CTR may rack completely the details of the manufacturers of the ingredients under clinical trials.

At the end of the day both the CTR architecture based system users and eCTD architecture based system users miss critical data contained in the other system despite the fact that both architectures are normally implemented in the same regulatory authority. It is important that a study of the two data architectures is done to ensure that as much as possible data integration from both architectures is achieved and relevant policy decisions are made to alter the therapeutic products regulation processes to maximise information benefits to the pharmaceutical industry and all users of the different architectures.

## 1.2 Research Objective

### *1.2.1 General Objective*

The main goal of the study is to investigate the suitability of implementing an integrated eCTD and CTR architecture at the Pharmacy and Poisons Board and examine its effects on the therapeutic product dossier submission, evaluation, clinical trials, non-clinical trials, pre-market authorization and post-market authorization surveillance of therapeutic products.

### *1.2.2 Specific Objectives*

1. Review the therapeutic products dossier submission and evaluation process and the eCTD data architecture .
2. Review the clinical and non-clinical trials management process and the CTD data architecture.
3. Propose an effective, efficient therapeutic products regulation process
4. Propose the implementation of an integrated data architecture in the therapeutic products regulatory process.
5. Propose the design of the integrated data architecture.

### *1.2.3 Issues to be addressed*

1. eCTD and CTR architectures were designed for niche systems, can they be integrated?
2. At what stage can successful completion of clinical trials be determined and the data can then be evaluated by a joint team of product registration and clinical trials departments?
3. Are there any policy changes that are needed?
4. Is this integration viable in terms of database implementation implications, policy implications, change management and business processes re-engineering at the organisation level?
5. What is the implication of the new integrated system in relation to international standards especially in regards to changes in policy and versions of the database and interface?
6. Should we propose an application interface level integration, or data architecture changes or both?

## 1.3 Research Questions

This research is aimed at investigating the suitability of implementing an integrated eCTD and CTR architecture in the therapeutic products regulation process at the Pharmacy and Poisons Board. The study attempts to answer the research questions:

1. Process of therapeutic products regulation?
2. Is the integration of eCTD and CTR data architectures possible?
3. How can the eCTD and CTR data architectures be integrated?
4. Is the integration of eCTD and CTR data architectures necessary?

5. What are the merits and demerits of integration of eCTD and CTR data architectures?

## 1.4 Justification

The primary ingredient of any regulatory activity is information. Getting this information from different sources with different processes and at times different philosophies is an odious task to itself. It would be very nice if all information was available from same source with high convenience. This study aims at assessing the benefits that Pharmacy and Poisons Board would derive from implementing an integrated eCTD and CTR data architecture and propose integrated data architecture to be implemented. In so doing this will provide documentation of the implementation of eCTD and CTR data architectures, a proposed integrated data architecture, the merits and demerits of an integrated data architecture and then give information technology experts and policy makers the knowledge on integration of eCTD and CTR data architectures and the implementation requirements.

## 1.5 Scope

### *1.5.1 Implementation Scope*

eCTD and CTR implementation covers the areas of clinical trials, therapeutic product dossier submission, evaluation, subsequent registration and post market authorization surveillance. The scope of this study aims to cover all the aspects of clinical trials, clinical trials registration, clinical trials evaluation, clinical trials monitoring and evaluation, dossier preparation, submission, receipt, first evaluation, second evaluation, plenary evaluation, therapeutic product rejection or approval and archiving of evaluation information. It will involve Pharmacy and Poisons Board's dossier evaluators, clinical trial regulation managers, information technology experts at the Pharmacy and Poisons Board.

### *1.5.1 Theory Scope*

This study will also focus on the study of integrating the two data architectures (eCTD and CTR) to form a new architecture that incorporates the two architectures. This study will not attempt to do a database schema merge but will attempt to design a completely new schema based on a new architecture.

## 1.6 Definition of Terms

Common Technical Document - Document format that defines what contents are required in the therapeutic products dossier and in which order.

Data Architecture – is composed of models, policies, rules or standards that govern which data is collected, and how it is stored, arranged, integrated, and put to use in data systems and in organizations.

Data Repository – is a somewhat general term used to refer to a destination designated for data storage. However, many IT experts use the term more specifically to refer to a particular kind of setup within an overall IT structure, such as a group of databases, where an enterprise or organization has chosen to keep various kinds of data.

Data Schema – refers to the organization of data as a blueprint of how a database is constructed (divided into database tables in case of Relational Databases)

Dossier – a group of papers that contain detailed information about someone or something

Efficacy – the ability to produce a desired or intended result.

Extensible Markup Language - is a markup language created to structure, store, and transport data by defining a set of rules for encoding documents in a format that is both human-readable and machine-readable.

market authorisation holder – Company or entity authorised to sell or trade in a registered therapeutic product.

Medicines Regulatory Authorities – these are government agencies in each country in the world that are designated and mandated to oversee the control of therapeutic products in their respective countries.

Model System for Computer Assisted Drug Registration (SIAMED) - Software used in therapeutic product registration and evaluation.

Pharmacology – the branch of medicine concerned with the uses, effects, and modes of action of drugs.

Pharmacovigilance – Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

Principal Investigator – Lead researcher in a clinical trial.

Study Data Tabulation Model – document format that defines data requirement of clinical trials study.

Therapeutic Product dossiers - a document that describes a drug or medicine, its ingredients, manufacturing processes and owners.

Therapeutic products - is a substance which may have medicinal, intoxicating, performance enhancing or other effects when taken or put into a human body or the body of another animal and is not considered a food or exclusively a food.

## 1.7 Assumptions

This study was based on the following assumptions:

1. That Kenya is obliged to implement international standards and best practices through various treaties, agreements and memoranda of understanding.
2. That Kenya has participatory rights to international standards and can contribute technically to those standards for adoption worldwide.
3. That the systems users are qualified professionals with sufficient training and experience in the user of the product regulation systems and clinical trials systems and understand the data requirements of the architectures.

## 1.8 Limitations of the Study

The accuracy of data in the eCTD and CTR architecture based system is partially determined by the design of the interface and partially by the accuracy and proficiency of the user, and therefore the accuracy of the final data found in databases designed using any architecture may not be used as an indicator of the success of an architecture or failure of the same.

# CHAPTER TWO – LITERATURE REVIEW

## 2.0 Literature Review

### *2.0.1 Pharmacy and Poisons Board, Kenya – source (Pharmacy and Poisons Board, 2008)*

**Mandate**

The Pharmacy and Poisons Act, Cap 244 is an Act of parliament to make better provision for the Control of the Profession of Pharmacy and trade in drugs and poisons.

The Pharmacy and Poisons Board is established as a body corporate, under the Pharmacy and Poisons Act, Cap 244 Laws of Kenya. The PPB is regulatory body within the Ministry of Medical Services. It is a body corporate under Section 3(6), and the de-linking process is on-going.

**Vision**

To be a Global Centre of Regulatory Excellence.

**Mission**

Safeguard the health of the public by ensuring that medicines and health products comply with acceptable standards of quality, safety and efficacy.

**Membership of the Pharmacy and Poisons Board**

The Board Members consists of the following:

Chairman - Director of Medical Services

Registrar - Chief Pharmacist

Director of Veterinary Services or Veterinary Surgeon nominated by him.

Four Pharmacists nominated by the Pharmaceutical Society of Kenya of whom

One shall be from the Civil Service

One shall be from Community Pharmacy

One shall be from the Pharmaceutical Industry

A representative from the Faculty of Pharmacy University of Nairobi.

A Pharmaceutical Technologist.

**Services**

The Board offers the following services:

1. Product Evaluation and Registration
2. Evaluation of Applications for Advertisements of Medicines and Medical Devices
3. Ensuring Good Manufacturing Practice (GMP)
4. Registration of Pharmacists
5. Enrolment of Pharmaceutical Technologists
6. Issuance of Annual Practice Licenses
7. Issuance of Annual Permits for Pharmaceutical Representatives
8. Approval of Institutions Offering Pharmacy Training Programmes
9. Approval of Pharmaceutical Imports and Exports
10. Registration of Pharmaceutical Premises/Outlets
11. Pharmacovigilance and Post-Market Surveillance
12. Documentation and Information Services on Medicines and Pharmacy Practice
13. Public relations services for the pharmaceutical sector
14. Regulation of Clinical Trials

**Clients**

1. Pharmaceutical Manufacturing Companies
2. Pharmaceutical Importers, Exporters, Distributors, Wholesalers, and Retailers
3. Hospitals and Healthcare Providers
4. Researchers
5. Pharmacy Practitioners
6. Universities and Colleges Offering Pharmacy Training
7. Pharmaceutical Services Providers
8. Consumers

**STAKEHOLDERS**

1. Government Ministries and Departments
2. Development Partners
3. Pharmaceutical Society of Kenya (PSK)
4. Kenya Pharmaceutical Association (KPA)
5. Other relevant Professional Organizations and Bodies
6. External Quality Assurance Agencies
7. Research Organizations
8. Industry and Private Sector

9. Students pursuing training in pharmacy
10. Consumers
11. The Public

### *2.0.2 Clinical Trials*

Clinical trials have been described as the holy grail of medicines development and testing process. The goal of a clinical trial is to develop safe and effective therapies efficiently. Early in development, investigators need to learn about the pros and cons of the drug in order to prepare for upcoming phases and determine if the drug is a worth pursuing. "During drug development, sponsors need to recognize safety signals early and adjust the development program accordingly, so as to facilitate the assessment of causality. Once a product is marketed, sponsors add post approval clinical trial data to the body of information to help understand existing safety concerns or those that arise from other post approval data sources, such as spontaneous reports" (Berlin, Crowe, Whalen, Xia, Koro, & Kuebler, 2013).

### *2.0.3 Therapeutic Product Development Process (Drug Development)*

A therapeutic product development process commonly referred to as drug development can be divided into four major step areas:

1. Drug Discovery
2. Pre-clinical Research
3. Clinical Research
4. Market Authorisation

During Drug Discovery researchers discover the active ingredients of a product either through identifying the active ingredient from traditional remedies or by serendipitous discovery. These form New Chemical Entities (NCEs). NCEs will have promising activity against a particular biological target thought to be important in disease; however, little will be known about the safety, toxicity, pharmacokinetics and metabolism of this NCE in humans.

The NCEs then move to Pre-Clinical Research where number of tests designed to determine the major toxicities of a novel compound prior to first use in man. It is a legal requirement that an assessment of major organ toxicity be performed (effects on the heart and lungs, brain, kidney, liver and digestive system), as well as effects on other parts of the body that might be affected by the drug (e.g. the skin if the new drug is to be delivered through the

skin). While, increasingly, these tests can be made using in vitro methods (e.g. with isolated cells), many tests can only be made by using experimental animals, since it is only in an intact organism that the complex interplay of metabolism and drug exposure on toxicity can be examined. In summary the Pharmacy and Poisons Board describes this as the "Non-Human studies of product development."

Clinical Research has four phases in Kenya:
Phase I - Human pharmacology – The purpose of these trials is to obtain preliminary data on safety of investigational products such as medicines or vaccines, or devices. These studies are carried out in a small number of healthy volunteers.

Phase II - Therapeutic exploratory – The purpose of these trials is to demonstrate therapeutic activity of medicines, or immunogenicity of vaccines, and to determine appropriate dose ranges or regimens. In addition, these trials obtain additional safety data. These studies are routinely carried out in patients. They are frequently split into two phases IIA (proof of Concept) and IIB (Dose finding). These studies provide early efficacy data.

Phase III - Therapeutic confirmatory – These are large trials aimed at determining efficacy of the investigational product. Generally, the conditions under which these trials are carried out should be as close as possible to normal conditions of use. The information obtained in this phase and the other two phases is used for licensure of the investigational product. Safety data is also collected in Phase III Trials. Phase IIIB are studies conducted just before or during regulatory filing to provide evidence to support product claims and to demonstrate safety in larger and more diverse populations.

Phase IV - Therapeutic use – These are studies performed after registration of the medicinal product for use by the general public. It is often referred to as Post-Marketing Surveillance Studies, these are studies designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with the widespread use.

The final stage is Market Authorisation.

### *2.0.4 Market Authorization for a Therapeutic Product*

This is the process of receiving, reviewing and evaluating a dossier of a therapeutic product with a view of ascertaining the quality, safety and efficacy of a product and granting or rejecting to grant a document called Market Authorization (also product license). The process of evaluating a dossier is done under a legislative framework that defines the competent (legally mandated) authority and evaluation process that provides the grounds for approval, rejection of application and withdrawal, suspension or revocation of issued license (Medicines and Healthcare Products Regulatory Agency, 2013).

Marketing authorization process is referred to by different names in different jurisdictions. In Kenya it is referred to as the Drug Registration Process, in the United States of America it is referred to as New Drug Application (NDA) and in the European Union as Market Authorization Application (MAA).

Figure 1: Therapeutic Product Evaluation Process Map, demonstrates the product registration process at Pharmacy and Poisons Board. It starts with an applicant submitting a dossier which goes through a checking and validation process that ensure only good products are evaluated and subsequently registered.

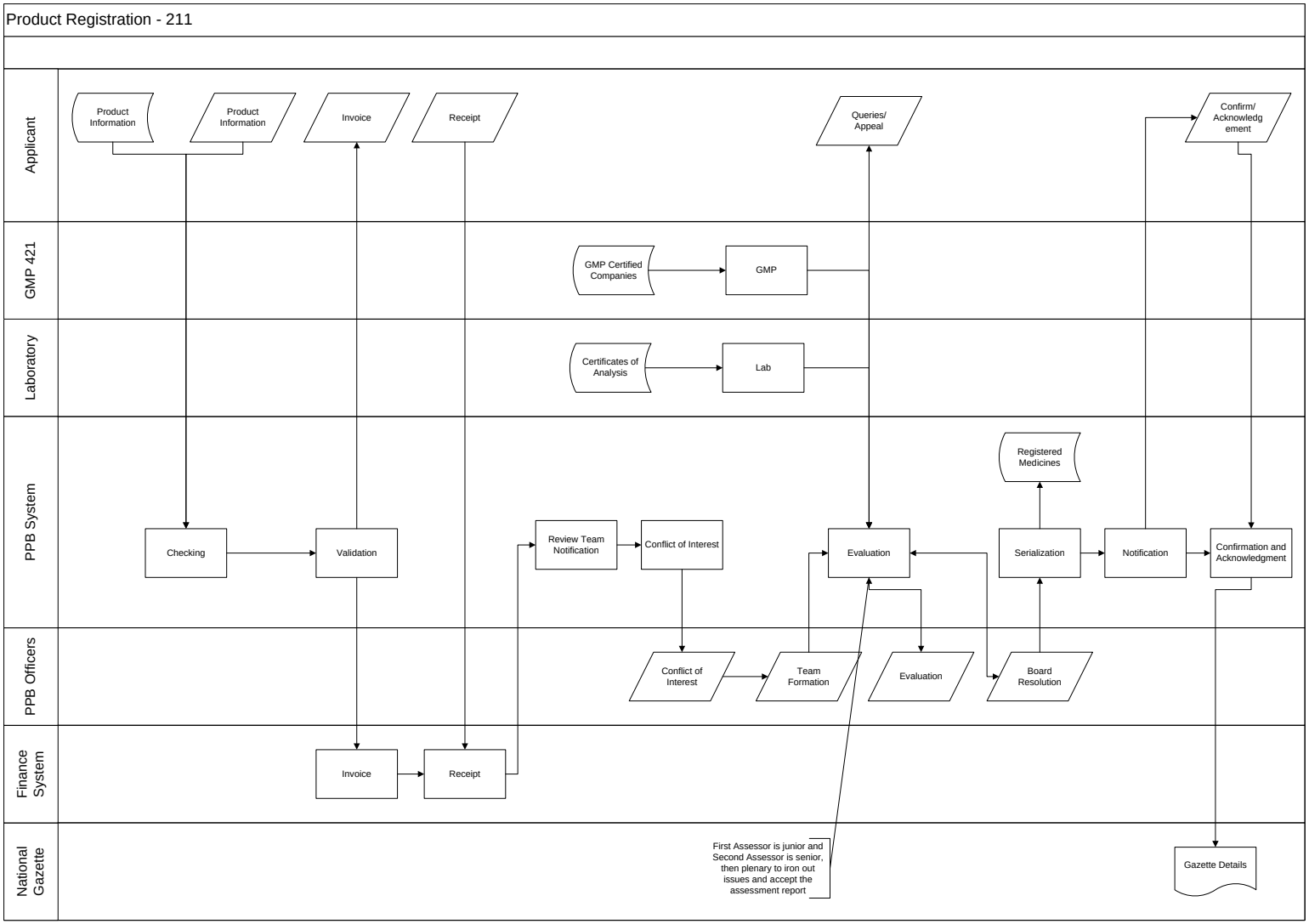


**Figure 1: Therapeutic Product Evaluation Process Map**

### *2.0.5 Clinical Trials Enforcement in Kenya*

The Pharmacy and Poisons Board is the national drug regulatory authority in Kenya established under Cap 244 Laws of Kenya. The importance of Research and Development in the attainment of national health, social and economic goals is well recognized. The Pharmacy and Poisons Board as the national drug regulatory authority has the mandate to ensure that clinical trials involving the use of new investigational drugs and older drugs for new conditions or diseases or investigational devices in human subjects are in compliance with national regulations including procedures to protect the safety of all participants (Pharmacy and Poisons Board, Kenya, 2011).

### *2.0.6 Clinical Trials*

Clinical Trials are important in helping discover new medicines to diagnose, treat, manage or prevent the many diseases affecting the human beings. The studies are also used to determine whether to change the initial indications, dosage or even the age group of the initially approved medications (Pharmacy and Poisons Board Kenya, 2012). Clinical trials are undertaken to allow data on the safety and efficacy of new products to be collected. These trials can be conducted using healthy volunteers or patients, depending on the type of product and its stage of development. Information on the non-clinical safety will have been obtained before the clinical trial programme commences.

To support the registration of these medicines, the studies need to be carried out according to the approved protocols. These studies should also be monitored/inspected to ensure the integrity of the data generated. In addition, these studies should be conducted in accordance with the regulatory requirements and Good Clinical Practices (GCP) standards.

Clinical trials begin with small studies in a controlled population of healthy volunteers or patients and, as data are gathered, expand to large-scale studies in patients. These large-scale studies will often investigate the new product and the currently used treatment to see how these two compare. As information is obtained, larger numbers of patients are exposed to the new product and safety data can be collected showing the safety of the product in the intended patient population.

In Kenya the Pharmacy and Poisons Board as the National Medicines Regulatory Authority, regulates Clinical Trials taking place in the country. The sponsors, prospective researchers or principal investigators should apply to the Board after obtaining Ethical favourable opinion / approval from one of the National Council for Science and Technology (NCST) – accredited ethical committees. In addition one needs to make his / her application by completing the prescribed application form and ensuring that all the requirements as indicated in the checklist are met (Pharmacy and Poisons Board Kenya, 2012).

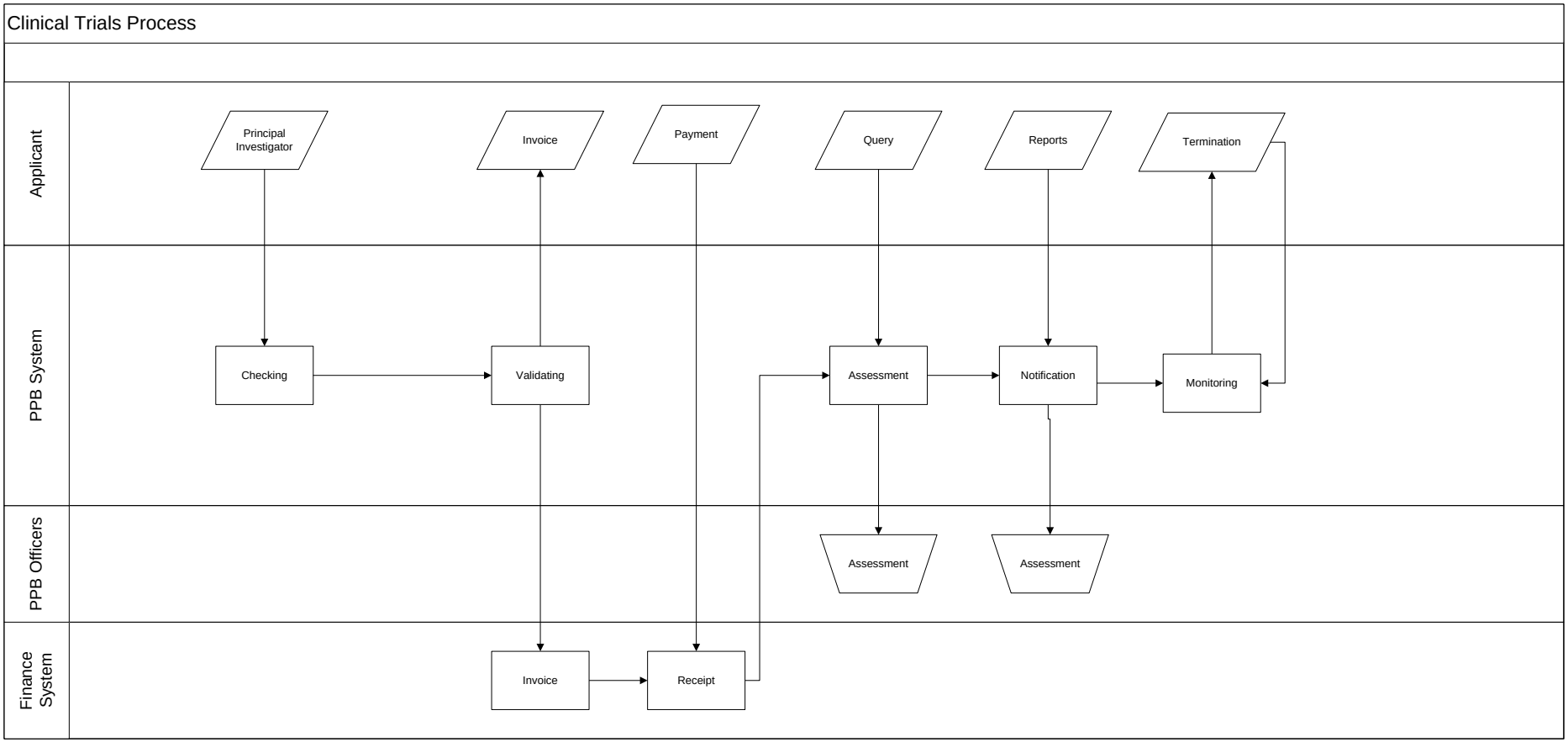


**Figure 2: Clinical Trials Process Map**

Figure 2: Clinical Trials Process Map, demonstrates how clinical trials are managed in Kenya. It starts with an applicant, normally the Principal Investigator submitting a protocol that goes through checking, validating and assessment. Once allowed to proceed with clinical trials, monitoring of the clinical trial then begins and continues through out the entire trial period.

### *2.0.7 Managing Clinical Trials Data – Study Data Tabulation Model (SDTM)*

Clinical trial data is stored using the Study Data Tabulation Model (SDTM) that defines a standard structure for human clinical trial (study) data tabulations and for nonclinical study data tabulations that are to be submitted as part of a product application to a regulatory authority such as the Pharmacy and Poisons Board. The Clinical Data Interchange Standards Consortium (CDISC) has a Submission Data Standards team that defines the SDTM which though not mandatory at the moment, it is expected will be used for all submissions in the future and all data managers will need to become proficient in SDTM.

SDTM is built around the concept of observations collected about subjects who participated in a clinical study. Each observation can be described by a series of variables, corresponding to a row in a dataset or table. Each variable can be classified according to its Role. A Role determines the type of information conveyed by the variable about each distinct observation and how it can be used. Variables can be classified into four major roles:

- Identifier variables, which identify the study, subject of the observation, the domain, and the sequence number of the record
- Topic variables, which specify the focus of the observation (such as the name of a lab test)
- Timing variables, which describe the timing of the observation (such as start date and end date)
- Qualifier variables, which include additional illustrative text, or numeric values that describe the results or additional traits of the observation (such as units or descriptive adjectives).

A fifth type of variable role, Rule, can express an algorithm or executable method to define start, end, or looping conditions in the Trial Design model.

The set of Qualifier variables can be further categorized into five sub-classes:

- Grouping Qualifiers are used to group together a collection of observations within the same domain. Examples include --CAT and --SCAT.
- Result Qualifiers describe the specific results associated with the topic variable for a finding. It is the answer to the question raised by the topic variable. Examples include --ORRES, --STRESC, and --STRESN. Many of the values in the DM domain are also

classified as Result Qualifiers.

- Synonym Qualifiers specify an alternative name for a particular variable in an observation. Examples include --MODIFY and --DECOD, which are equivalent terms for a --TRT or --TERM topic variable, --TEST and --LOINC which are equivalent terms for a --TESTCD.
- Record Qualifiers define additional attributes of the observation record as a whole (rather than describing a particular variable within a record). Examples include --REASND, AESLIFE, and all other SAE (serious adverse event) flag variables in the AE domain; and --BLFL, --POS and --LOC, --SPEC, --LOT, --NAM.
- Variable Qualifiers are used to further modify or describe a specific variable within an observation and is only meaningful in the context of the variable they qualify. Examples include --ORRESU, --ORNRHI, and --ORNRLO, all of which are variable qualifiers of --ORRES, and --DOSU and --DOSFRM, all of which are variable qualifiers of --DOSE.

In the current situation, to store clinical trials data, each regulatory authority develops its own format that is based on the SDTM taking into account the data elements that regulatory authority needs captured. Mostly this is done to simplify the application, submission and evaluation process. The main data elements are:

- Protocol Number;
- Protocol Title;
- Drug Name;
- Medical Condition;
- Study population;
- Date of No Objection Letter;
- Sponsor Name;
- Control Number;
- Study Start Date;
- Study End Date;
- Trial Status.

These data elements are normally designed to meet the data requirements of section four of the eCTD data requirements. Pharmacy and Poisons Board has developed its data format that has fifteen sections and very many data elements that the principal investigator is expected to fill in a format known as the Clinical Trials Registry (CTR).

### *2.0.8 Storing Clinical Trials Data*

The need to maintain clinical trials data stores that contribute to the body of knowledge can never be over emphasized. To maintain a competitive position, the biopharmaceutical industry has been facing the challenge of increasing productivity both internally and externally. As the product of the clinical development process, clinical data are recognized to be the key corporate asset and provide critical evidence of a medicine's efficacy and safety and of its potential economic value to the market. It is also well recognized that using effective technology-enabled methods to manage clinical data can enhance the speed with which the drug is developed and commercialized, hence enhancing the competitive advantage. The effective use of data-capture tools may ensure that high-quality data are available for early review and rapid decision-making. A well-designed, protocol-driven, standardized, site workflow-oriented and documented database, populated via efficient data feed mechanisms, will ensure regulatory and commercial questions receive rapid responses. When information from a sponsor's clinical database or data warehouse develops into corporate knowledge, the value of the medicine can be realized. Moreover, regulators, payer groups, patients, activist groups, patient advocacy groups, and employers are becoming more educated consumers of medicine, requiring monetary value and quality, and seeking out up-to date medical information supplied by biopharmaceutical companies. All these developments in the current biopharmaceutical arena demand that clinical data management (CDM) is at the forefront, leading change, influencing direction, and providing objective evidence (Lu & Su, 2010).

### *2.0.9Adoptions of Study Data Tabulation Model (SDTM)*

Adoptions of the SDTM to suit specific implementation needs are quite common. At the moment that is fine as the SDTM has not officially become a mandatory standard. However it is important that the adoption does not deviate from the SDTM standard but essentially becomes subset data architecture of SDTM. The Pharmacy and Poisons Board has adopted CTR and some companies like Johnson and Johnson have established translational and biomarker departments and implemented an effective knowledge management framework including building a data warehouse and the associated data mining applications (Szalma, Koka, Khasanova, & Perakslis, 2010).

### *2.0.10 Enforcement of SDTM at the Federal Drug Authority*

The Federal Drug Authority (FDA) of the United States of America (USA) - PPB equivalent in the USA - is using eCTD as the basis for implementing and enforcing the use of SDTM. This is very important as it enables to FDA to use patient profiles in SDTM during market authorization evaluation done in eCTD. For years, patient profiles were instrumental in conveying information and data about a single patient in a concise output within a company's submission to FDA. In the clinical trial world of eCTD and SDTM, the need for these outputs has decreased because when data submitted is SDTM compliant the FDA has a powerful graphical patient profile tool to review the data. What is now a benefit of FDA receiving SDTM domains leaves other stakeholders within the sponsor company creating the submission without outputs that many groups find essential to do their work. Through experience, there is still a need for the creation of simple patient profiles to meet operational objectives when conducting clinical trials, creating the submission documents, and making patient safety decisions (Peterson & Ramalingam, 2010). This is true taking into account complex patient profiles don't have any proven value addition in data management.

### *2.0.11 Clinical Data Interchange Standards Consortium (CDISC)*

CDISC is a global, open, multidisciplinary, non-profit organization that has established standards to support the acquisition, exchange, submission and archive of clinical research data and metadata. The CDISC mission is to develop and support global, platform-independent data standards that enable information system interoperability to improve medical research and related areas of healthcare (Clinical Data Interchange Standards Consortium, 2013). CDISC defines the SDTM standards.

CDISC standards are – source (Clinical Data Interchange Standards Consortium, 2013):

- Study Data Tabulation Model (SDTM)
- Study Data Tabulation Model SDTM Implementation Guide (SDTM-IG)
  Gives a standardized, predefined collection of submission metadata "Domains" containing extensive variable collections.
- Analysis Data Model (ADaM)
  Designed to complement the SDTM submission by detailing the statistical analysis performed on the clinical trial results.
- Standard for Exchange of Non-clinical Data (SEND)
  The animal trial equivalent of SDTM.
- Operational Data Model (ODM)
  The highlights of ODM: includes audit trail, utilizes XML technology, machine- and human- readable, all information are independent from

databases, storing of ODM is independent from hard- and software.

- Laboratory Data Model (LAB)

  The Lab standard is used for exchange of laboratory data between labs and CROs

- Case Report Tabulation Data Definition Specification (CRT-DDS)

  Also referred to as "define.xml", a machine-readable version of the regulatory submission "define.pdf".

- Clinical Data Acquisition Standards Harmonization (CDASH)

  Defines a minimal data collection set for sixteen safety SDTM Domains, harmonizing element names, definitions and metadata. The objective is to establish a standardized data collection baseline across all submissions.

- CDISC Terminology

  Defines controlled terminology for SDTM and CDASH, provides extensible lists of controlled terms designed to harmonize data collected across submissions.

### *2.0.12 International Conference on Harmonisation (ICH)*

The International Conference on Harmonisation's electronic Common Technical Document (eCTD) endeavours to significantly change the pharmaceutical submission process. After decades of using paper, the goal is the electronic transfer of drug applications and their review across submission formats, procedures, and regions (Suchanek & Ostermann, 2012).

The ICH has four major parts:

1. ICH Steering Committee
2. ICH Coordinators
3. ICH Secretariat
4. ICH Working Groups

The Steering Committee, made of six ICH Parties, governs the ICH, determining the policies and procedures, selecting topics for harmonisation and monitoring progress of harmonisation initiatives. The ICH consists of:

1. European Commission
2. European Federation of Pharmaceutical Industries and Associations (EFPIA)
3. Ministry of Health, Labour and Welfare (Japan)
4. Japan Pharmaceutical Manufacturers Association (JPMA)
5. Food and Drug Administration (FDA)
6. Pharmaceutical Research and Manufacturers of America (PhRMA)

The ICH Coordinators represents each ICH Party to the ICH Secretariat on a day-to-day basis.

The ICH Secretariat is primarily concerned with preparations for, and documentation of, meetings of the Steering Committee as well as coordination of preparations for Working Group (EWG, IWG, Informal WG) and Discussion Group meetings.

The ICH Working Groups are created by the Steering Committee when a new topic is accepted for harmonisation, and is charged with developing a harmonised guideline that meets the objectives outlined in the Concept Paper and Business Plan.

Face-to-face meetings of the EWG will normally only take place during the biannual SC meetings. Interim reports are made at each meeting of the SC.

If consensus is reached the EWG will sign the Step 2 Experts Signoff sheet and submit it to the SC to request adoption. If there is no agreement in the EWG within the time frame the SC may extend the time frame, suspend or abandon the harmonization project(Clinical Data Interchange Standards Consortium, 2013).

### *2.0.13 Generics*

Generic are therapeutic products is defined as a drug product that is comparable to brand/reference listed drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use (Federal Drug Authority, USA, 2013). In the generics industry, the submission management process and the document management system should therefore be adapted to support this process of dossier creation and post-application management of hundreds, or even thousands, of dossiers. In order to effectively implement this process, it is highly recommended that a document management system be configured in such a way that every individual document is stored in the system only once. The most effective integration of a document management system and publishing system will enable production of a CTD or eCTD from the same initial documents. This will enable companies to support the submission process in cases where only paper submission is needed, only electronic, or both.

### *2.0.14 Common Technical Document (CTD) and Electronic CTD (eCTD)*

The Pharmaceutical industry very much aware of the disharmony in regulation of therapeutic

product dossiers for evaluation, requested the three main regional entities where most of the new medicines were being registered to harmonise the submission and evaluation process. In 1990 an agreement between European Union, Japan and the United States of America formed the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use to create standards for various pharmaceutical regulation areas mainly therapeutic product registration and adverse drug reporting. At the initial stages the ICH came up with standards for the Common Technical Document (CTD) format to be used in therapeutic product dossier submission and the Data Elements for Transmission of Individual Case Safety Report E2B(R2) format (ICH, International Conference for Harmonisation, 2012).

The CTD has five modules:

1. Administrative Information and Prescribing Information
2. Common Technical Document Summaries
3. Quality
4. Nonclinical Study Reports
5. Clinical Study Reports

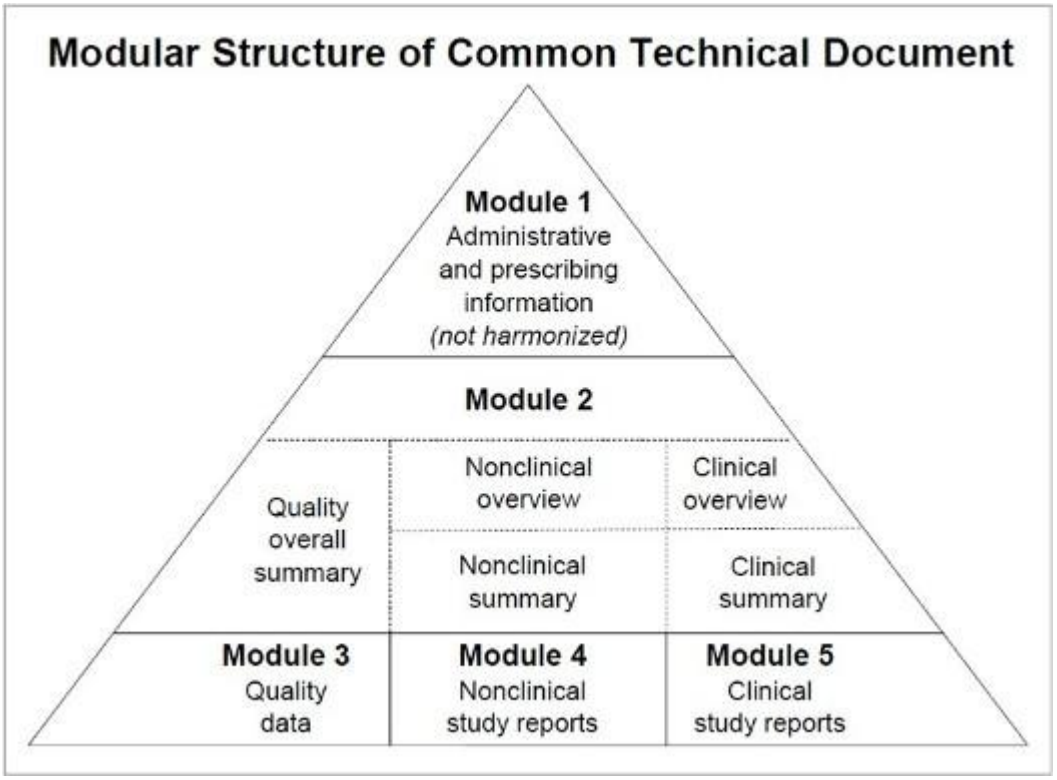


**Figure 3: Modular Structure of Common Technical Document**

In March 2010, Pharmacy and Poisons Board adopted the CTD as the official dossier preparation, submission and evaluation format. This was to make therapeutic product registration better and meet international standards and best practices.

To fully implement the CTD format, the Pharmacy and Poisons Board needed software that would help in managing the submissions and the evaluation process. The Board identified Model System for Computer Assisted Drug Registration (SIAMED), which was already available as the starting software. SIAMED had all the features necessary for drug registration but had the following weaknesses:

1. It lacked support from the vendor. This was due to the fact that the software had been developed as a donation from WHO organisation and the recipient countries were expected to support its upgrade that never happened.
2. It used out dated substance dictionaries.
3. It was impossible to upgrade to fully implement eCTD. The developers of the system could not be accessed either.

In order to overcome the challenges identified with SIAMED the Board decided to build its own software to meet the International Committee on Harmonisation (ICH) M8 eCTD standards. This was achieved easily and the pharmaceutical industry was happy to use the new architecture that made their work easy. In October 2012 pharmaceutical industry started to submit their therapeutic product dossiers in the eCTD format on Compact Disc (CD) or Digital Versatile Disks (DVD).

Though the eCTD format has been extolled by both the pharmaceutical industry and the regulators as the epitome of therapeutic product dossier submission and evaluation, questions from information technology experts linger as to whether the eCTD format as designed by the ICH multi-disciplinary working group code M8 is sufficient enough, for its intended purpose. For instance, the eCTD as designed does not offer facility for full text search which limits the search to the meta data found in the Extensible Markup Language (XML) submission backbone.

### *2.0.15 Electronic Common Technical Document (eCTD)*

The electronic Common Technical Document (eCTD) is defined as an interface for industry to agency transfer of regulatory information, while at the same time taking into consideration the facilitation of the creation, review, lifecycle management and archival of the electronic submission. eCTD is just an ‘envelope’ that will enable industry to communicate and

exchange information easily and should be considered only as the final step in the process of generating an electronic submission (Nordfjeld & Strasberger, 2006).

### *2.0.16 Electronic Solutions Enforcement*

The pharmaceutical industry and institutions have undertaken lots of efforts to enforce the electronic solutions. They focus on international standards in order to harmonise structures and processes. It would be necessary to reduce paper and copies, especially if the electronic solution takes place. This method will simplify the way to deal with data and documents and reduce process time and costs (Esslinger & Marschall, 2006).

### *2.0.17 Benefits of eCTD*

Optimal eCTD is based on solid integrated document management architecture. However, it is still unclear whether implementing eCTD really brings more advantages than disadvantages. Suchanek and Ostermann conducted interviewsin 2010 on behalf of the European Medicines Agency on 963 experts and 397. The responses that were used for subsequent study analysis indicated that three-fourths majority of those with eCTD experience reported disadvantages in implementing eCTD. An overwhelming majority of the same group reported advantages that outweighed the disadvantages, some of them significantly. More than three-quarters of individuals with eCTD experience were able to shorten their total time to approval. More than 90% of this group was able to demonstrate cost savings relative to paper submissions, regardless of their company kind, size, or number of submissions(Suchanek & Ostermann, 2012).

All over the world, drugs and drug applications have to be submitted to and approved by an admission office before they may be sold on the market. All procedures are extensive, time consuming, and costly. To simplify the process, it could be organised electronically. In an economic perspective, there are many benefits by using the electronic form for the pharmaceutical industry: managing knowledge, cost advantages, and time savings.

### *2.0.18 Data Architectures*

The data architecture is the set of specifications, rules, and processes that dictate how data is stored in a database and how data is accessed by components of a system. It includes data types, relationships, and naming conventions. The data architecture describes the organization of all database objects and how they work together. It affects integrity,

reliability, scalability, and performance. The data architecture involves anything that defines the nature of the data, the structure of the data, or how the data flows. It also gives models, policies, rules or standards that govern which data is collected, and how it is stored, arranged, integrated, and put to use in data systems and in organizations(Lewis G. , Comella-Dorda, Place, Plakosh, & Seacord, 2001).

Data architecture defines how data is stored, managed, and used in a system. In particular, data architecture describes

• how data is persistently stored
• how components and processes reference and manipulate this data
• how external/legacy systems access the data
• interfaces to data managed by external/legacy systems
• implementation of common data operations(Lewis G. A., Comella-Dorda, Place, Plakosh, & Seacord, 2001)

The data architecture is a high-level design that cannot always anticipate and accommodate all implementation details (actual database designs). Some of these details may impose demands that conflict with the data architecture. In these cases, it may be necessary to re-evaluate the data architecture to determine what can be done to accommodate the additional demands. It is also allowable to violate the data architecture in places, as long as the rationale for doing so is well understood, well documented, and does not compromise the robustness, performance, and integrity of the overall system.

### *2.0.19Schema Merging*

It involves combining data residing in different sources and providing users with a unified view of these data. The theory of Schema Merging forms a subset of database theory and formalizes the underlying concepts of the problem in first-order logic. Applying the theories gives indications as to the feasibility and difficulty of Schema Merging(Kwakye, Kiringa, & Viktor, 2013).

A database schema is the description of a database, for example, the entity-relationship model. Batini et al define schema integration as “the process of merging several conceptual schemas into a global conceptual schema that represents all the requirements of the

application". Schema integration is used to merge two or more database schemas into a single schema that can store data from both the original databases. Schema integration is used when two or more existing databases must be combined, for example, when a new management information system is being developed. Schema integration may be used when the process of database design istoo large to be carried out by one individual. Two or more designers will build models of different parts of the database and use schema integration to merge the resulting models. There are two major types of schema integration:

• View Integration View integration takes place during the design of a new database when user requirements may be different for each user group. View integration is used to merge different viewpoints into a single data model.

• Database Integration Database integration is used when two or more databases must be combined to produce a single schema, called a global schema.

In this study as indicated earlier, combining of data residing in different sources will not be done or proposed, instead a new design of data architecture will be proposed.

## 2.1 Legal and Electronic StandardsLimitations and Proposed Solution

### *2.1.1 Legal and International Standards Limitations to Regulatory Automation*

Laws and standards governing clinical trials are based on traditional approaches. Kenyan law, CAP 244 does not explicitly require clinical trials to be part of the therapeutic products evaluation.

*9. (1) The Board shall, before registering a new drug for which the research work has been conducted in another country and its efficacy, safety, and quality established in that country, require an investigation on the pharmaceutical, pharmacological and other aspects of the drug to be conducted and clinical trials to be made which are necessary to establish its quality and where applicable the biological availability and its safety and efficacy to be established under local conditions.*

*(2) Notwithstanding paragraph (1), the Board may register a new drug and require the investigations and clinical trials specified in paragraph (1) to be conducted after its registration.* (Laws of Kenya, 2009)

This is due to the fact that traditionally Kenya has had no strong clinical trials culture and very few medicines have their clinical trials done in Kenya. However in the electronic age it does not matter where the clinical trials were done, the data can be stored in repositories in Kenya and accessed from Kenya irrespective of the geographical location of the researcher. Therefore using information technology Pharmacy and Poisons Board can demand to monitor clinical trials happening elsewhere without necessary having to be physically present.

Electronic Common Technical Document is a replica of the paper based Common Technical Document with a few additions to describe how computers will be required to handle the data. In doing so it is assumed that the entire process will follow the paper based process only with the paper missing. Due to the manner in which CTD was developed through negotiations between industry players and government agencies, it was just pragmatic to smoothly transits from paper based system to an electronic system without causing any major changes that may have a negative impact in terms of revenue and expenditures to any party.

What this transition mean therefore is, clinical trials and therapeutic products evaluations continued to be managed as they were done before. The major outcome of this was the existence of two repositories that were as traditional as they ever were and data exchanged between these two repositories in the same way papers were exchanged between departments. To this date countries have to implement the two repositories like to completely different paper stores. In more developed countries, the departments dealing the two areas exist as completely independent government agencies, and internationally the governing bodies, that is CDISC and ICH are completely independent of each other.

Though this is good to improve and manage international standards, a complete review of the electronic enabling environment is needed to harmonise data management irrespective of the users of the data. The two agencies (CDISC and ICH) and the different department can continue to exist separately and manage their standards separately but have a harmonised data management standard that increases efficiency and effectiveness of data management. Shared data repositories and data standards does not mean diminished capacity of either entity but a better working platform.

### *2.1.2 Proposed Solution*

Data architecture integration involves bringing together two different data architectures to function as one unified architecture. It includes the change or development of new rules, policies, schemas and repositories to accommodate the integrated data architecture. Data Architecture Integration can also be loosely equated to data architecture design where new data architecture is developed the only difference being that in integration the new architecture is based on pre existing architectures that do not cease to exist once the new architecture comes into place.

Since the eCTD and CTR data architectures are based on international standards that have a gradual but predetermined change path, the first proposal for implementation of the new Data Architecture will be to re-engineer the business processes in Clinical Trials and Market Authorisation to recognise different data capture, data statuses, data utilisation points and data uses. For example, clinical trials data can be used for a new process to be named – Pre-Market Authorisation Evaluation – that is not in existence now, and policy changes to review therapeutic product evaluator specialisations and relevant experience of dossier evaluators which is not the case at present.

The proposed solution is to integrate the two data architectures that is eCTD and CTR (based on SDTM) and have companies submit their clinical trials data directly into a repository that also accommodates eCTD. The reason for this being the Kenya law does not explicitly require the Board to regulate clinical trials and only requires clinical trials to be part of the therapeutic product registration.

*9. (1) The Board shall, before registering a new drug for which the research work has been conducted in another country and its efficacy, safety, and quality established in that country, require an investigation on the pharmaceutical, pharmacological and other aspects of the drug to be conducted and clinical trials to be made which are necessary to establish its quality and where applicable the biological availability and its safety and efficacy to be established under local conditions.*

*(2) Notwithstanding paragraph (1), the Board may register a new drug and require the investigations and clinical trials specified in paragraph (1) to be conducted after its registration.* (Laws of Kenya, 2009)

Having one repository with different data architectures will be beneficial to the Board since the Board will have managed to meet international requirements and laws of Kenya at the same time.

FDA of USA has similar integration of the SDTM and eCTD architectures: however the repositories are separate and the submissions are done differently. This partly is because the use is highly dependent on innovator molecules or newly discovered drugs. Kenya on the other hand is highly dependent on clinical trials done in other countries and use of generic medicines, which means it would be best if the submission is done at once and into one repository but with separation of architectures in order to meet international standards.

This research proposes integrating the two architectures into one repository as a good practice for Kenya as it meets the legal requirements of Kenya and the international standards. It is good to note that the international standards do not dictate how the repository will finally be implemented but the format of data in the repository.

# CHAPTER THREE - METHODOLOGY

## 3.0 Methodology

### *3.0.1 Introduction*

The methodology for this study will be two steps:

1. Analysing of the data architectures of the eCTD and CTR and establish the data elements in both data architectures. Shared data elements will be identified and non-shared data elements will also be identified. Non-shared data elements will be analysed for similarities between the two formats in:
    a. Naming conventions used.
    b. Data types used.
    c. Data field equivalents.
    d. Data field sequences.
    e. How data is collected for the data elements.
2. Develop an integrated data architecture to incorporate the two data architectures taking into account:
    a. Possible Data Schema.
    b. Possible Implementation guidelines.
    c. Possible Policy Requirements.
    d. Possible Processes Re-engineering.

## 3.1 Research Design

This is a desk review based research with unstructured interview with eCTD and CTD users at Pharmacy and Poisons Board and East Africa Community Medicines registration authorities.

Documents used in the regulation of clinical trials and therapeutic products evaluation will be perused to understand and map the processes. Data flow diagrams will also be made from the mapped processes in order to completely visualise the entire information management aspect of the regulatory process. Based on these information proper inferences, proposals and recommendations will be made.

## 3.4 Research Instruments

### *3.4.1 List of Instruments*

Various instruments will be used in the research. These are:

1. Desk review of eCTD and CTR architectures design and implementation policy documents, architectures design documentation and implementation reports (if available). Items to be reviewed under desk review are:
    a. ICH guidance on implementation of eCTD.
    b. ICH eCTD specifications version 3.2.2.
    c. Pharmacy and Poisons Board and East Africa Community (EAC) eCTD specifications draft version.
    d. Pharmacy and Poisons Board Standard Operating Procedures for Product Evaluation version 1
    e. Pharmacy and Poisons Board guidelines for product application and submission year 2010 version
    f. Pharmacy and Poisons Board eCTD specifications documents version 1.0
    g. CDISC SDTM implementation guideline version 3.1.2 (Specifications contained inside the guide)
    h. Pharmacy and Poisons Board CTR specifications version 1.0
    i. Pharmacy and Poisons Board Clinical Trials Guideline of February 2011
2. Microsoft Visio for process mapping of Clinical Trials Processes and Therapeutic Products Registration Processes.
3. MySQL Workbench for data architecture visualisation.
4. Microsoft Excel for data elements analysis

### *3.4.2 Desk Review Instruments Structure*

1. Document Analysis

| Document | Version | Date Published | Publisher | Data Architecture | Data Collection Methods | Naming Conventions Used | Data Types Used | Data Fields | Data Field Sequences |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | |

**Table 1: Document Analysis Tool**

Explanation of the Tool

| TOOL ITEM | DESCRIPTION | EXAMPLE |
|---|---|---|
| Document | The document under review | ICH eCTD specifications version 3.2.2 |
| Version | Version of document under review | 3.2.2 |
| Date Published | Date document was published | 16th July 2008 |
| Publisher | Owner of document | ICH |

| | | |
|---|---|---|
| Data Architecture | The architecture described in the Document | eCTD |
| Data Collection Methods | Methods for collecting data using the architecture | Typing, Machine to Machine |
| Naming Conventions Used | Naming conventions the document recommends | Too many for an example |
| Data Types Used | Various types of data that can be used | Text, Numbers, Alpha-Numeric |
| Data Fields | The actual fields where the data will go | Too many for an example |
| Data Field Sequences | How the data fields are ordered | Too many for an example |

**Table 2: Document Analysis Tool Explanation**

2. Data Fields analysis tools

| **eCTD Field ID** | **eCTD Field Name** | **eCTD Field Data Structure** | **CTR Field ID** | **CTR Field Name** | **CTR Field Data Structure** | **Data Connection between eCTD and CTD data Fields** | **Proposed Data Structure** |
|---|---|---|---|---|---|---|---|
| | | | | | | | |

**Table 3: Data Fields Analysis Tool**

Explanation of tool

| **TOOL ITEM** | **DESCRIPTION** | **EXAMPLE** |
|---|---|---|
| eCTD Field ID | eCTD Fields with data sources in CTR | Not Possible due to nature of data fields |
| eCTD Field Name | | |
| eCTD Field Data Structure | | |
| CTR Field ID | CTR Fields for creating data for eCTD | |
| CTR Field Name | | |
| CTR Field Data Structure | | |
| eCTD and CTR Fields data connection | Proposed integration of data. | |
| Proposed Data Structure | | |

**Table 4: Data Fields Analysis Tool Description**

## 3.5 Instrument Pre-test

Both architectures and the intended architecture have administrative information sections that provide for summary data of the submission to be done. The administrative information is used to inform the evaluator of a clinical trials or therapeutic products application who the applicant is and what the application contains. Administrative information is different in both architectures and can be used to pre-test the tools since they contain very little information unlike the complete architectures.

## 3.6 Data Collection

Data necessary for this exercise will be obtained from the desk review where the researcher will get the designs of the eCTD and CTR data architectures.

Further unstructured interview will be conducted with stakeholders (drug registration department and clinical trials department users) from the Pharmacy and Poisons Board of Kenya and since East Africa Community specifications will be used, discussions will also be held with heads of ICT departments of Tanzania Food and Drug Regulatory Authority, National Drug Authority of Uganda, Rwanda Pharmacy Taskforce, Burundi Pharmacy Taskforce, Zanzibar Food and Drug Authority and the East Africa Health Harmonisation ICT head from Arusha Tanzania. Members of the East Africa Medicines Harmonisation Technical Work Group will also participate in the discussions.

The unstructured interview will focus on:

1. User experiences on automation of therapeutic product evaluation and clinical trial processes.
2. User experiences with the eCTD and CTR data architectures or their equivalent.
3. Proposals they would wish to see implemented should any of the architectures change.

Schedule of Pharmacy and Poisons Board and East African Community meetings is as follows:

| **DATES** | **MEETING** | **VENUE** | **Sponsor** |
|---|---|---|---|
| 26/09/2013 to 27/09/2013 | EAC Stakeholders meeting | Sarova Panafric Nairobi | EAC and Pharmacy and Poisons Board |
| 21/10/2013 to 09/11/2013 | EAC Information Management Systems Technical Working Group – E-Readiness Assessment | Head offices of Medicines Regulatory Authorities of the six EAC partner states | EAC and Medicines Regulatory bodies of EAC partner States |
| 22nd October 2013 | Pharmacy and Poisons Board automation review workshop | Olive Gardens Hotel | Pharmacy and Poisons Board. |

**Table 5: Schedule of Meetings Schedules**

## 3.7 Data Analysis

Once all the data has been collected, analysis will be done using the tools shown in 3.4.2 Desk Review Instruments Structure, process maps, policy documents review and with inputs from the unstructured interviews to:

1. Document a detailed documentation of existing Clinical Trials and Therapeutic Products Evaluation processes.
2. Capture the design of the eCTD and CTR architecture designs
3. Demonstrate the implementation of eCTD and CTR architecture implementation at Pharmacy and Poisons Board.
4. Propose effective, efficient clinical trial and therapeutic products evaluation processes.
5. Proposed possible architecture interfacing modalities.

# CHAPTER FOUR – eCTD AND CTR DATA ARCHITECTURES

## 4.0 Introduction

This chapter organizes, presents and explains the data collected and desk review findings established in this study. Data on Information Communication Technologies (ICT) status of Pharmacy and Poisons Board and all regulatory bodies in the East Africa Community (EAC) was obtained using a questionnaire and visits to the regulatory bodies. All processes of Medicines Evaluation and Registration were reviewed as well as the tools used in the Medicines Evaluation and Registration. The same was also done for Clinical Trials. Data on the status of National Medicines Regulatory Authorities (NMRA) in their capacity to implement eCTD and CTR was collected from the NMRAs of EAC. Finally desk review was done on the eCTD and CTR standards documents and policy documents used in the implementation of the two standards in Kenya's Pharmacy and Poisons Board. To enable better understanding of the frameworks and standards, descriptions have been incorporated from the ICH and CDISC standards documents.

## 4.1 eCTD

This section is extracted verbatim from ICH eCTD Standard Version 3.2.2 and is meant to help the reader of this report better understand the eCTD.

### *4.1.1 eCTD Standard Introduction*

The eCTD is an interface for industry to regulatory agency transfer of regulatory information while taking into consideration the facilitation of the creation, review, life cycle management and storing of the electronic submission. The eCTD specification lists the criteria that will make an electronic submission valid. The focus of the specification is to provide the frameworkof registration application submission electronically from industry to a regulatory authority.

The eCTD specification is based upon content defined within the CTD given by the ICH M4 Expert Working Group (EWG). The CTD describes modules, sections and documents organisation for submission. The structure and level of detail specified in the CTD have been used as the basis for defining the eCTD structure and content but, where appropriate, additional details have been developed within the eCTD specification.

The philosophy of the eCTD is to use open standards. Open standards, including proprietary standards that through their widespread use can be considered de facto standards, are deemed to be appropriate in general.

### *4.1.2 Scope of ICH eCTD Standard Version 3.2.2.*

The M4 EWG defined CTD covers only module two to module five. Countries or regions are expected to define module one including all the documents to be submitted. eCTD therefore also covers the same areas covered by CTD and the rules of CTD wholly apply to eCTD.

### *4.1.3 eCTD Standard Technical Requirements*

The specification is designed to support high-level functional requirements such as the following:Copy and paste, viewing and printing of documents, annotation of documentation, facilitate the exporting of information to databases, searching within and across applications and navigation throughout the eCTD and its subsequent amendments/variations.

### *4.1.4 eCTD Standard Business Model*

The business process to be supported can be described as follow:

Industry <-----> Message <------> Agency

The business process defines specific requirements for the message. The eCTD Specification currently provides only a transport mechanism for one-way traffic from applicant to agency.

The primary focus of the eCTD is to provide a data interchange message between industry and agencies. Industry initiates the process by creating the initial submission in terms of an electronic CTD. Throughout the life cycle of this process, additional information will be submitted to update or modify the information contained in the initial submission (e.g., supplement, amendment, variation.) The agency can submit acknowledgements, queries and requests to industry. These are considered simple messages using electronic mail or other transport formats. The overall architecture of the eCTD is designed to provide a commonly agreed upon submission and submission structure that imposes minimal restriction to the industry and agencies.

### *4.1.5 eCTD Standard Modular Structure*

eCTD format is standardised to match CTD and submission contents should always match.

### *4.1.6 eCTD Standard: XML Based eCTD*

The overall structure of the submission is defined by the XML eCTD Document Type Definition (DTD). Its purpose is:

(1) to manage submission and document meta-data

(2) to provide table of contents for navigation.

The XML instance of any submission is defined in the XML eCTD DTD ICH eCTD version 3.2.2 for creation and validation.

The ICH M4 Expert Working Group XML eCTD DTD describes the hierarchical structure of the CTD. It includes multiple hierarchical levels depending on the specific module and can include more hierarchical levels below those defined in the CTD. The XML eCTD instance covers the entire submission.The submission should include a Stylesheet that supports presentation of the XML instance.

### *4.1.6 eCTD Standard Lifecycle Management*

This varies from agency to agency but principally the applicant submits initial submission into the agency repository and the agency moves that submission to another repository for evaluation. The applicant can submit other updates such as queries, edits, amendments and variations. Updates can refer to previous submissions or documents in previous submissions. The XML backbone should provide navigation aids to filter the different submission types.

Though the entire submission is electronic, some parts are still submitted physically like signatures that are regional requirements.

### *4.1.7 eCTD Standard Submission*

The eCTD submission is composed of the following:

- Structure of directory
- The XML eCTD instance
- Document content files

### *4.1.8 eCTD Standard Directory Structure*

The directory structure is a structure of directories and files similar to operating system directories. The naming and management is similar to that of operating system directories with the XML backbone carrying the meta data of the directories.

### *4.1.9 eCTD Standard XML eCTD Instance*

The submission sequence number directory should contain at least two files and one or more directories. One of the files in the submission sequence directory should be the instance and the other should be the MD5 checksum of the instance. The instance is the starting file for the processing by an XML processor.

The intention is to have links from the leaf elements of the instance to the files in the eCTD submission as opposed to creating a single XML document that contains the entire eCTD submission. The instance also contains meta-data at the leaf level.

### *4.1.10 eCTD Standard eCTD Template*

The ICH Web site (http://estri.ich.org/eCTD) includes an empty eCTD folder template as an example of an eCTD submission folder structure. It shows all of the possible Module 2-5 folders and can be populated with the applicant data and edited as appropriate (i.e., adding additional subfolders or removing unnecessary folders). The applicant should still add the relevant country Module 1 folders and content, add the appropriate utility folders and content, and create the XML index files to complete a valid eCTD submission.

### *4.1.11 eCTD Standard Formats*

Formats are supposed to be readable at least for as long as it is needed for the regulatory process. This process could be very long (e.g., 50 years). This points to the advantage of neutral formats: formal standard, industrial standard, vendor independent, and text-like. The format is adapted to the type of data.

The list of agreed to formats is updated as technology evolves and new requirements arise. XML is the preferred format for all types of data.

### *4.1.12 eCTD Standard Common Formats*

The common formats that can be included in an eCTD submission are:

- Narrative: Portable Document Format (PDF)
- Structured: Extensible Markup Language (XML)
- Graphic: Whenever possible, PDF is preferred. When appropriate or when PDF is not possible, Joint Photographic Experts Group (JPEG), Portable Network Graphics (PNG), Scalable Vector Graphics (SVG), and Graphics Interchange Format (GIF) can be used. Special formats for very high resolutions could be appropriate on a case-by-case basis.

### *4.1.13 eCTD Standard Regional Use of Formats*

Regulatory authorities and applicants can agree to use other formats regionally (i.e., non-common formats or uses of the common formats in a different way from above). The use of other formats isdiscouraged and the intention is to use as much as possible the common formats. The intention of the use of other formats is for transition purposes.

There are two classes of transitions:

- Legacy Transition: from the past to the present (i.e., old formats to present formats.)
- Future Transition: from the present to the future (i.e., from present formats to new formats.) The new formats would normally be candidates for common formats.

### *4.1.14 eCTD Standard Links*

CTD cross-references can be supported in the eCTD through the use of hyperlinks. Links among objects inthe eCTD submission are relative. The intention is to make the eCTD submission self-contained. All literature references introduced by the applicant are included in the submission.

One can always point to a file. The capacity to point to a specific location within a file depends on the linking technology. Different formats allow for the use of different linking technology.

### *4.1.15 eCTD Standard Presentation*

Presentation is closely associated with formats. To associate a Stylesheet with a file usually one has to use alinking technology. The linking between Stylesheet (which could be in a

separate file) and a data fileshould be relative. In addition, there is the dimension of media. One file could have several Stylesheets; the one used depends on the media. For example, there could be one presentation for the screen and another for paper.

### *4.1.16 eCTD Standard Checksums*

The eCTD submission contains checksums for each individual file including a checksum file for theeCTD XML instance. Initially, the MD5 Message-Digest Algorithm (MD5)would be used for this purpose. Including a checksum for each individual file provides a number of benefits including:

- The integrity of each file can be verified by comparing the checksum submitted with the file and the computed checksum.
- The checksum can be used to verify that the file has not been altered in the historical archive of the regulatory authority. This is especially useful as the files are migrated from one storage medium to another, as in the case of backup to magnetic tape storage.

### *4.1.17 eCTD Standard Element to File Directory Mapping*

The following rules are recommended:

- The rules below for the file and directories take precedence.
- Add the corresponding extension to the file.
- If appropriate, use a reasonable abbreviation.

### *4.1.18 eCTD Standard File Extension*

All files have one and only one file extension. The file extension can be used to indicate the format of the file. For example:

hello.pdf PDF

hello.rtf RTF

The mapping between formats and extensions are: IANA nomenclature

text/css text/html html or htm text/xml xml application/pdf pdf application/rtf rtf application/vnd.ms-excel xls image/jpeg jpg image/png png image/gif gif

Non IANA nomenclature

DTD dtd XPT (SAS) xpt XSL xsl

The eCTD submission uses formats not registered with the Internet Assigned Numbers Authority(IANA).

### *4.1.19 eCTD Standard Name*

Name is a token composed of the following characters:

- Letters "a" to "z" [U+0061 to U+007A].
- Digits "0" to "9" [U+0030 to U+0039].
- "-" [HYPHEN-MINUS, U+002D].

The notation "U+" refers to the Unicode [UNICODE] notation.

This Specification does not provide for Japanese characters in file and folder names.

Examples of correct names (only the name without the extension):

part-b

myfile hello

Examples of incorrect names (only the name without the extension):

part a (' ' ; SPACE is not allowed)

myfile.xml ('.' ; FULL STOP is not allowed) hello:pdf (':' ; COLON is not allowed) part_a (‘_’, LOW LINE is not allowed) Parta (UPPERCASE is not allowed)

Directory name is a name.

File name is one name followed by one name separated by a
'.' (FULL STOP, U+002E).

Correct file names (with the extension):

myfile.pdf hello.cml

Incorrect file names (with the extension):: a part.pdf (' '; SPACE is not allowed) hello (missing extension)

hello:xml (':'; COLON is not allowed)

The maximum length of the name of a single folder or file is 64 characters including the extension. Only lower case letters are used in all file and directory names. The maximum length of a path is 230 characters, including file name, and extension. This allows regulators 26 characters to add to the path in their review environments. If the path exceeds the 230 character limit or the regionally-defined limit, then folder and file namescreated by the applicant are abbreviated. If further reduction is still called for, the file and folder names recommended in are abbreviated.

Document name is the first name in the file name. For example, “docname” in the file name “docname.ext”.

#### *4.1.20 eCTD Standard Character Encoding*

The character encoding (charset) in order of preference is:

- Unicode UTF-8, Unicode 16 bits [ISO-10646].
- ISO-8859-1 (Latin-1) or appropriate ISO-8859-x; e.g., ISO-8859-7 for Greek.
- The appropriate SHIFT_JIS.
- Other character encoding agreed upon regionally by the regulatory authority and applicant.

## 4.2 eCTD Modules

#### *4.2.1 eCTD Module Introduction*

eCTD has five modules. Module One (1) has regional or national information and his defined by the country or region. In Kenya Module One is defined by the Pharmacy and Poisons Board and regionally in the EAC, countries have agreed to adopt the Kenya definition of Module one with minor adjustments.

Modules two (2) to Module five (5) are defined internationally and are adopted as they are. In Kenya they have been adopted as they are and the same has been done for the EAC.

With the EAC adopting what Kenya has done, the Kenyan implementation will not be affected by the regional standards and will only face challenges due to differences in implementation status in different countries.

Since the focus is the use of eCTD in Kenya and the EAC harmonisation comes in as a possible influence to the Kenyan implementation, the eCTD to be explained is as implemented in Kenya.

### *4.2.2 eCTD Structure*

#### 4.2.2.1 Folder and File Naming Conventions

Folder and file names have a maximum 64 characters including the extension and are written in lower case only.

| Description | File Name |
|---|---|
| Study Report1 | *study-report-1.pdf* |
| Study Report2 | *study-report-2.pdf* |
| … | ... |
| Study Reportn | *study-report-n.pdf* |

**Table 6: Folder and File Naming Conventions**

#### 4.2.2.2 Module 1 Administrative Information and Prescribing Information

The name of the folder for module 1 will be m1. This module contains administrative information that is unique for each country or region. Below is the Kenyan version.

| **MODULE 1: ADMINISTRATIVE INFORMATION** | |
|---|---|
| **SECTION 1: PARTICULARS OF THE PRODUCT** | |
| **1.1 Name and address of Applicant** | |
| 1.2 | Trade Name of the product (Proprietary Product Name) |
| 1.3 | International Non-proprietary Name (INN) of the Active Pharmaceutical Ingredient (API) |
| 1.4 | Strength of Active Pharmaceutical Ingredient (API) per unit dosage of the product: |
| 1.5 | Pharmaceutical Dosage form and route of administration of the product |
| 1.5.1 | Pharmaceutical Dosage form of the product: |
| 1.5.2 | Route*(s)* of administration (use current list of standard terms - European Pharmacopoeia) |
| 1.6 | Packing of the product/: |
| 1.6.1 | Pack size of the product |
| 1.7 | Visual description of the product |
| 1.8 | Proposed shelf life (in months): |
| 1.8.1 | Proposed shelf life (after reconstitution or dilution): |
| 1.8.2 | Proposed shelf life (after first opening container): |

| | |
|---|---|
| 1.8.3 | Proposed storage conditions: |
| 1.8.4 | Proposed storage conditions after first opening: |
| 1.9 | **Pharmacotherapeutic group and ATC Code** |
| **1.9.1** | **Pharmacotherapeutic group:** |
| **1.9.2** | **ATC Code:** ***(Please use current ATC code)*** |
| **1.9.3** | **If no ATC code has been assigned, please indicate WHO ATC application reference number:** ☐ |
| **1.10** | **Legal category A** ☐ **B** ☐ **C**☐ |
| **1.11** | **Country of origin or country of release:** |
| 1.12 a | **Attach certificate of pharmaceutical product from competent regulatory authority** |
| 1.12 b | Product Marketing Authorisation in the country of origin and other countries. If not registered, state reasons |
| 1.13 | Pre-registration analysis of the product<br>(Attach certificate of analysis from a recognized WHO Prequalified Quality Control Laboratory in Kenya and within the Region) |
| 1.14 | Name(s) and complete address (s) of the manufacturer(s) |
| **1.14.1** | **Name(s) and complete address (s) of the manufacturer(s) of the Finished Pharmaceutical Product (FPP), including the final product release if different from the manufacturer** (add as many rows as necessary**)** |
| **1.14.2** | **Name(s) and complete address (s) of the manufacturer(s) of the active pharmaceutical ingredient(s) (API)**<br>(add as many rows as necessary**)** |
| **1.15.1** | **Good Manufacturing Practice (GMP) status of the manufacturer (s) of the FPP** |
| **1.15.2** | **Good Manufacturing Practice (GMP) status of the manufacturer (s) of the API(s)** |
| **1.16** | **Name and complete address of the Local Technical Representative of Manufacturer** |
| **1.17** | **Summary Product Characteristics (SPC)** |
| **1.18 Batch number(s) of the FPPs used (Add as many rows as necessary)** | |

**Table 7: Kenya's Module 1**

### 4.2.2.3 Module2Summaries (source ICH eCTD Standard Version 3.2.2)

The files in this module are provided as PDF text with the exception of a few embedded images,when needed. The name of the folder for module 2 is m2. The folders in module 2 are named as follows but can be further reduced or omitted to minimize path length issues.

| Sectionin CTD | Description | Folder Name |
|---|---|---|
| 2.2 | Introduction | *22-intro* |
| 2.3 | Quality overallsummary | *23-qos* |
| 2.4 | NonclinicalOverview | *24-nonclin-over* |

| | | |
|---|---|---|
| 2.5 | Clinical Overview | *25-clin-over* |
| 2.6 | NonclinicalWrittenand Tabulated Summaries | *26-nonclin-sum* |
| 2.7 | Clinical summary | *27-clin-sum* |

**Table 8: Module 2**

Arepresentativefolder hierarchy for module2ispresentedinthescreenshot in figure 3-1.

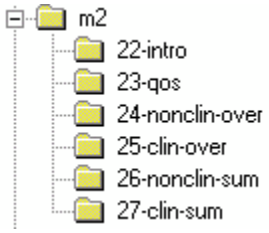


**Figure 4: Module 2 Folder Structure**

#### 4.2.2.4 Module3Quality (source ICH eCTD Standard Version 3.2.2)

The name of the folder for module 3 is m3. The folders in module 3 are named as follows butcan be further reduced or omitted to minimize path length issues.

| Sectionin CTD | Description | Folder Name |
|---|---|---|
| 3.2 | Bodyof Data | *32-body-data* |
| 3.2.S | Drug Substance | *32s-drug-sub* |
| 3.2.S | Drug Substance[Drug Substance Name] [Manufacturer]2 | *substance-1-manufacturer-1* |
| 3.2.S.1 | General Information(name,manufacturer) | *32s1-gen-info* |
| 3.2.S.2 | Manufacture(name,manufacturer) | *32s2-manuf* |
| 3.2.S.3 | Characterisation(name, manufacturer) | *32s3-charac* |
| 3.2.S.4 | Controlof DrugSubstance (name, manufacturer) | *32s4-contr-drug-sub* |
| 3.2.S.4.1 | Specification (name,manufacturer) | *32s41-spec* |
| 3.2.S.4.2 | Analytical Procedures(name,manufacturer) | *32s42- analyt-proc* |
| 3.2.S.4.3 | Validationof Analytical Procedures(name, manufacturer) | *32s43-val-analyt-proc* |
| 3.2.S.4.4 | BatchAnalyses(name,manufacturer) | *32s44-batch-analys* |
| 3.2.S.4.5 | Justificationof Specification(name, manufacturer) | *32s45-justif-spec* |
| 3.2.S.5 | ReferenceStandards orMaterials(name, manufacturer) | *32s5-ref-stand* |
| 3.2.S.6 | ContainerClosureSystem(name, manufacturer) | *32s6-cont-closure-sys* |
| 3.2.S.7 | Stability (name,manufacturer) | *32s7-stab* |

| | | |
|---|---|---|
| 3.2.P | Drug Product (name,dosage form)[3] | *32p-drug-prod* |
| 3.2.P | Drug Product (name,dosage form)-*Name* | *product-1* |
| 3.2.P.1 | Description andComposition of the Drug Product (name, dosage form) | *32p1-desc-comp* |
| 3.2.P.2 | Pharmaceutical Development(name,dosage | *32p2-pharm-dev* |

| Sectionin CTD | Description | Folder Name |
|---|---|---|
| 3.2.P.3 | Manufacture(name,dosage form) | *32p3-manuf* |
| 3.2.P.4 | Controlof Excipients (name,dosage form) | *32p4-contr-excip* |
| 3.2.P.4 | Controlof Excipients (name,dosage form)-*Excipient1* | *excipient-1* |
| 3.2.P.5 | Controlof DrugProduct (name,dosage form) | *32p5-contr-drug-prod* |
| 3.2.P.5.1 | Specification(s)(name,dosage form) | *32p51-spec* |
| 3.2.P.5.2 | Analytical Procedures(name,dosage form) | *32p52-analyt-proc* |
| 3.2.P.5.3 | Validationof Analytical Procedures(name, dosage form) | *32p53-val-analyt-proc* |
| 3.2.P.5.4 | BatchAnalyses(name,dosageform) | *32p54-batch-analys* |
| 3.2.P.5.5 | Characterisation of Impurities (name, dosage | *32p55-charac-imp* |
| 3.2.P.5.6 | Justification of Specifications (name,dosage | *32p56-justif-spec* |
| 3.2.P.6 | ReferenceStandards orMaterials(name,dosage | *32p6-ref-stand* |
| 3.2.P.7 | ContainerClosureSystem(name,dosage form) | *32p7-cont-closure-sys* |
| 3.2.P.8 | Stability (name,dosageform) | *32p8-stab* |
| 3.2.A | Appendices | *32a-app* |
| 3.2.A.1 | Facilities and Equipment (name,manufacturer) | *32a1-fac-equip* |
| 3.2.A.2 | AdventitiousAgents Safety Evaluation (name, | *32a2-advent-agent* |
| 3.2.A.3 | Excipients-*Name*[4] | *32a3-excip-name-1* |
| 3.2.R | Regional Information[5] | *32r-reg-info* |
| 3.3 | Literature References | *33-lit-ref* |

**Table 9: Module 3**

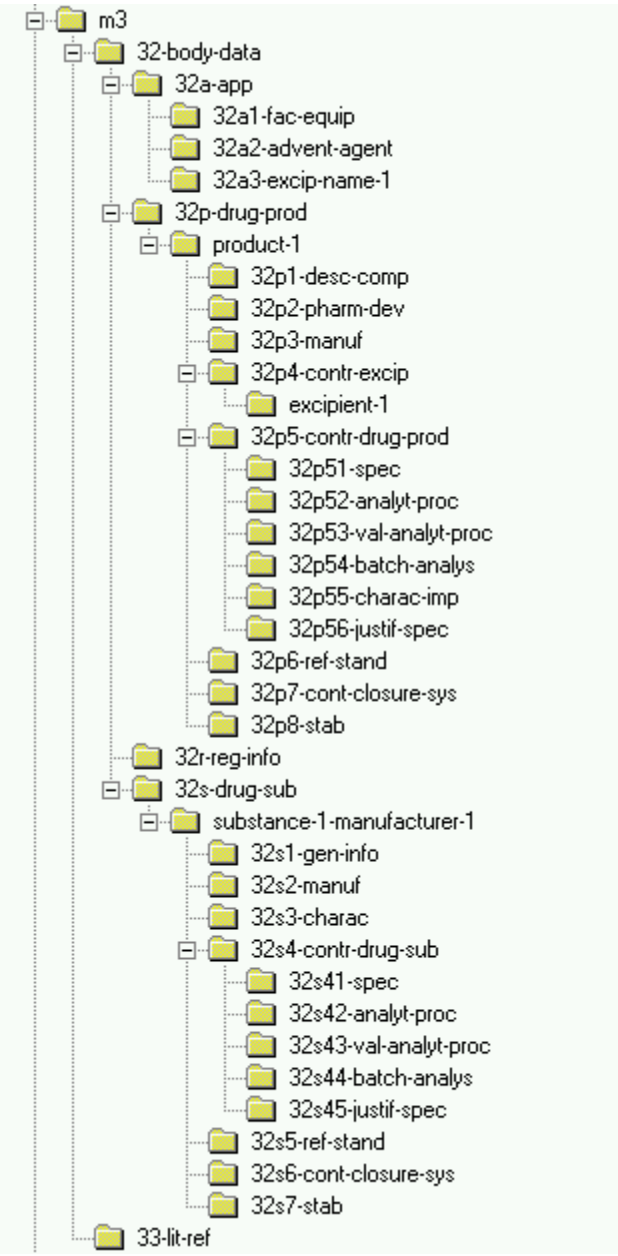


**Figure 5: Module 3 Folder Structure**

### 4.2.2.5 Module4NonclinicalStudyReports (source ICH eCTD Standard Version 3.2.2)

The name of the folder for module 4 is m4. The folders in module 4 are named as follows but can be further reduced or omitted to minimize path length issues.

**Table3-4**

| Section in CTD | Description | FolderName |
|---|---|---|
| 4.2 | Study Reports | *42-stud-rep* |
| 4.2.1 | Pharmacology | *421-pharmacol* |

| | | |
|---|---|---|
| 4.2.1.1 | Primary Pharmacodynamics | *4211-prim-pd* |
| 4.2.1.2 | Secondary Pharmacodynamics | *4212-sec-pd* |
| 4.2.1.3 | Safety Pharmacology | *4213-safety-pharmacol* |
| 4.2.1.4 | PharmacodynamicDrug Interactions | *4214-pd-drug-interact* |
| 4.2.2 | Pharmacokinetics | *422-pk* |
| 4.2.2.1 | Analytical Methodsand ValidationReports (if | *4221-analyt-met-val* |
| 4.2.2.2 | Absorption | *4222-absorp* |
| 4.2.2.3 | Distribution | *4223-distrib* |
| 4.2.2.4 | Metabolism | *4224-metab* |
| 4.2.2.5 | Excretion | *4225-excr* |
| 4.2.2.6 | Pharmacokinetic DrugInteractions | *4226-pk-drug-interact* |
| 4.2.2.7 | OtherPharmacokinetic Studies | *4227-other-pk-stud* |
| 4.2.3 | Toxicology | *423-tox* |
| 4.2.3.1 | Single-Dose Toxicity (in orderby species,by | *4231-single-dose-tox* |
| 4.2.3.2 | Repeat-Dose Toxicity (in orderby species,by route, byduration,including supportive | *4232-repeat-dose-tox* |
| 4.2.3.3 | Genotoxicity | *4233-genotox* |
| 4.2.3.3.1 | In vitro | *42331-in-vitro* |
| 4.2.3.3.2 | In vivo (including supportive toxicokinetics | *42332-in-vivo* |
| 4.2.3.4 | Carcinogenicity (includingsupportive toxicokineticsevaluations) | *4234-carcigen* |
| 4.2.3.4.1 | Long-termstudies(inorder by species, including range-findingstudiesthat cannotbe appropriately included underrepeat-dose toxicity or | *42341-lt-stud* |

| Section in CTD | Description | FolderName |
|---|---|---|
| 4.2.3.4.2 | Short-ormedium-termstudies(including range-findingstudies that cannotbeappropriately included under repeat-dosetoxicity or | *42342-smt-stud* |
| 4.2.3.4.3 | Otherstudies | *42343-other-stud* |
| 4.2.3.5 | Reproductive and Developmental Toxicity (including range-finding studiesandsupportive | *4235-repro-dev-tox* |
| 4.2.3.5.1 | Fertility andearly embryonicdevelopment | *42351-fert-embryo-dev* |

| | | |
|---|---|---|
| 4.2.3.5.2 | Embryo-fetal development | *42352-embryo-fetal-dev* |
| 4.2.3.5.3 | Prenatal and postnataldevelopment,including | *42353-pre-postnatal-dev* |
| 4.2.3.5.4 | Studies in whichthe offspring (juvenile animals)are dosedand/or furtherevaluated | *42354-juv* |
| 4.2.3.6 | Local Tolerance | *4236-loc-tol* |
| 4.2.3.7 | OtherToxicity Studies(ifavailable) | *4237-other-tox-stud* |
| 4.2.3.7.1 | Antigenicity | *42371-antigen* |
| 4.2.3.7.2 | Immunotoxicity | *42372-immunotox* |
| 4.2.3.7.3 | Mechanistic studies(if not | *42373-mechan-stud* |
| 4.2.3.7.4 | Dependence | *42374-dep* |
| 4.2.3.7.5 | Metabolites | *42375-metab* |
| 4.2.3.7.6 | Impurities | *42376-imp* |
| 4.2.3.7.7 | Other | *42377-other* |
| 4.3 | LiteratureReferences | *43-lit-ref* |

**Table 10: Module 4**

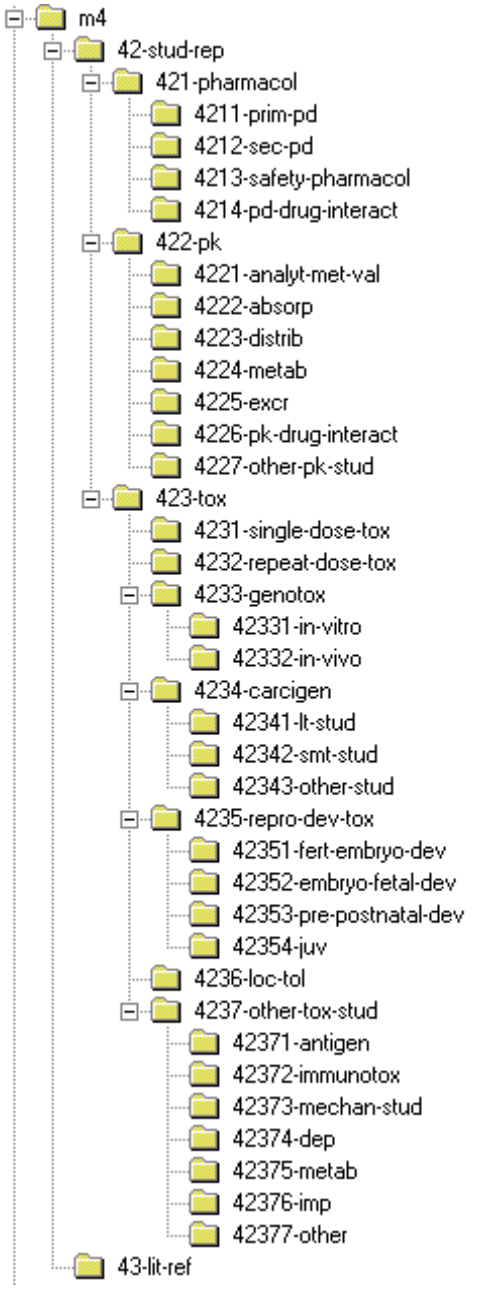


**Figure 6: Module 4 Folder Structure**

### 4.2.2.6 Module5Clinical StudyReports (source ICH eCTD Standard Version 3.2.2)

The name of the folder for module 5 is m5. The folders in module 5 are named as follows butcan be further reduced or omitted to minimize path length issues.

| Section in CTD | Description | FolderName |
|---|---|---|
| 5.2 | Tabular Listing of all Clinical Studies | *52-tab-list* |

| | | |
|---|---|---|
| 5.3 | Clinical StudyReports | *53-clin-stud-rep* |
| 5.3.1 | Reportsof Biopharmaceutic Studies | *531-rep-biopharm-stud* |
| 5.3.1.1 | Bioavailability(BA) Study Reports | *5311-ba-stud-rep* |
| | "Study Report1" | *study-report-1* |
| | "Study Report2" | *study-report-2* |
| | "Study Report3" | *study-report-3* |
| 5.3.1.2 | ComparativeBAand Bioequivalence(BE) Study Reports | *5312-compar-ba-be-stud-rep* |
| | "Study Report1" | *study-report-1* |
| | "Study Report2" | *study-report-2* |
| | "Study Report3" | *study-report-3* |
| 5.3.1.3 | In vitro – In vivo Correlation Study | *5313-in-vitro-in-vivo-corr-stud-rep* |
| | "Study Report1" | *study-report-1* |
| | "Study Report2" | *study-report-2* |
| | "Study Report3" | *study-report-3* |
| 5.3.1.4 | ReportsofBioanalytical andAnalytical Methods for HumanStudies | *5314-bioanalyt-analyt-met* |
| | "Study Report1" | *study-report-1* |
| | "Study Report2" | *study-report-2* |
| | "Study Report3" | *study-report-3* |
| 5.3.2 | Reportsof Studies Pertinentto Pharmacokineticsusing | *532-rep-stud-pk-human-biomat* |
| 5.3.2.1 | Plasma ProteinBinding StudyReports | *5321-plasma-prot-bind-stud-rep* |
| | "Study Report1" | *study-report-1* |
| | "Study Report2" | *study-report-2* |
| | "Study Report3" | *study-report-3* |

| **Section in CTD** | **Description** | **FolderName** |
|---|---|---|
| 5.3.2.2 | Reports of Hepatic MetabolismandDrug Interaction Studies | *5322-rep-hep-metab-interact-stud* |
| | "Study Report1" | *study-report-1* |
| | "Study Report2" | *study-report-2* |
| | "Study Report3" | *study-report-3* |
| 5.3.2.3 | Reports of Studies Using Other Human Biomaterials | *5323-stud-other-human-biomat* |
| | "Study Report1" | *study-report-1* |

| | | |
|---|---|---|
| | "Study Report2" | *study-report-2* |
| | "Study Report3" | *study-report-3* |
| 5.3.3 | Reports of HumanPharmacokinetic (PK) Studies | *533-rep-human-pk-stud* |
| 5.3.3.1 | Healthy Subject PK and Initial Tolerability | *5331-healthy-subj-pk-init-tol-stud-rep* |
| | "Study Report1" | *study-report-1* |
| | "Study Report2" | *study-report-2* |
| | "Study Report3" | *study-report-3* |
| 5.3.3.2 | Patient PK and Initial Tolerability Study Reports | *5332-patient-pk-init-tol-stud-rep* |
| | "Study Report1" | *study-report-1* |
| | "Study Report2" | *study-report-2* |
| | "Study Report3" | *study-report-3* |
| 5.3.3.3 | IntrinsicFactor PK Study Reports | *5333-intrin-factor-pk-stud-rep* |
| | "Study Report1" | *study-report-1* |
| | "Study Report2" | *study-report-2* |
| | "Study Report3" | *study-report-3* |
| 5.3.3.4 | ExtrinsicFactorPKStudy Reports | *5334-extrin-factor-pk-stud-rep* |
| | "Study Report1" | *study-report-1* |
| | "Study Report2" | *study-report-2* |
| | "Study Report3" | *study-report-3* |
| 5.3.3.5 | PopulationPK Study Reports | *5335-popul-pk-stud-rep* |
| | "Study Report1" | *study-report-1* |

| **Section in CTD** | **Description** | **FolderName** |
|---|---|---|
| | "Study Report2" | *study-report-2* |
| | "Study Report3" | *study-report-3* |
| 5.3.4 | Reports of HumanPharmacodynamic(PD) Studies | *534-rep-human-pd-stud* |
| 5.3.4.1 | Healthy Subject PDandPK/PDStudy | *5341-healthy-subj-pd-stud-rep* |
| | "Study Report1" | *study-report-1* |
| | "Study Report2" | *study-report-2* |
| | "Study Report3" | *study-report-3* |
| 5.3.4.2 | Patient PD and PK/PD StudyReports | *5342-patient-pd-stud-rep* |

| | | |
|---|---|---|
| | "Study Report1" | *study-report-1* |
| | "Study Report2" | *study-report-2* |
| | "Study Report3" | *study-report-3* |
| 5.3.5 | ReportsofEfficacy and Safety Studies | *535-rep-effic-safety-stud* |
| 5.3.5 | ReportsofEfficacy and Safety Studies–*IndicationName* | *indication-1* |
| 5.3.5.1 | Study Reports of Controlled Clinical Studies | *5351-stud-rep-contr* |
| | "Study Report1" | *study-report-1* |
| | "Study Report2" | *study-report-2* |
| | "Study Report3" | *study-report-3* |
| 5.3.5.2 | Study Reports of UncontrolledClinical | *5352-stud-rep-uncontr* |
| | "Study Report1" | *study-report-1* |
| | "Study Report2" | *study-report-2* |
| | "Study Report3" | *study-report-3* |
| 5.3.5.3 | Reports of Analysesof DatafromMorethan One Study | *5353-rep-analys-data-more-one-stud* |
| | "Study Report1" | *study-report-1* |
| | "Study Report2" | *study-report-2* |
| | "Study Report3" | *study-report-3* |
| 5.3.5.4 | OtherStudy Reports | *5354-other-stud-rep* |
| | "Study Report1" | *study-report-1* |

| Section in CTD | Description | FolderName |
|---|---|---|
| | "Study Report2" | *study-report-2* |
| | "Study Report3" | *study-report-3* |
| 5.3.6 | Reports of Postmarketing Experience | *536-postmark-exp* |
| 5.3.7 | CaseReport Formsand Individual Patient Listings | *537-crf-ipl* |
| | “Study Report1” | *study-report-1* |
| | “Study Report2” | *study-report-2* |
| | “Study Report3” | *study-report-3* |
| 5.4 | Literature References | *54-lit-ref* |

**Table 11: Module 5**

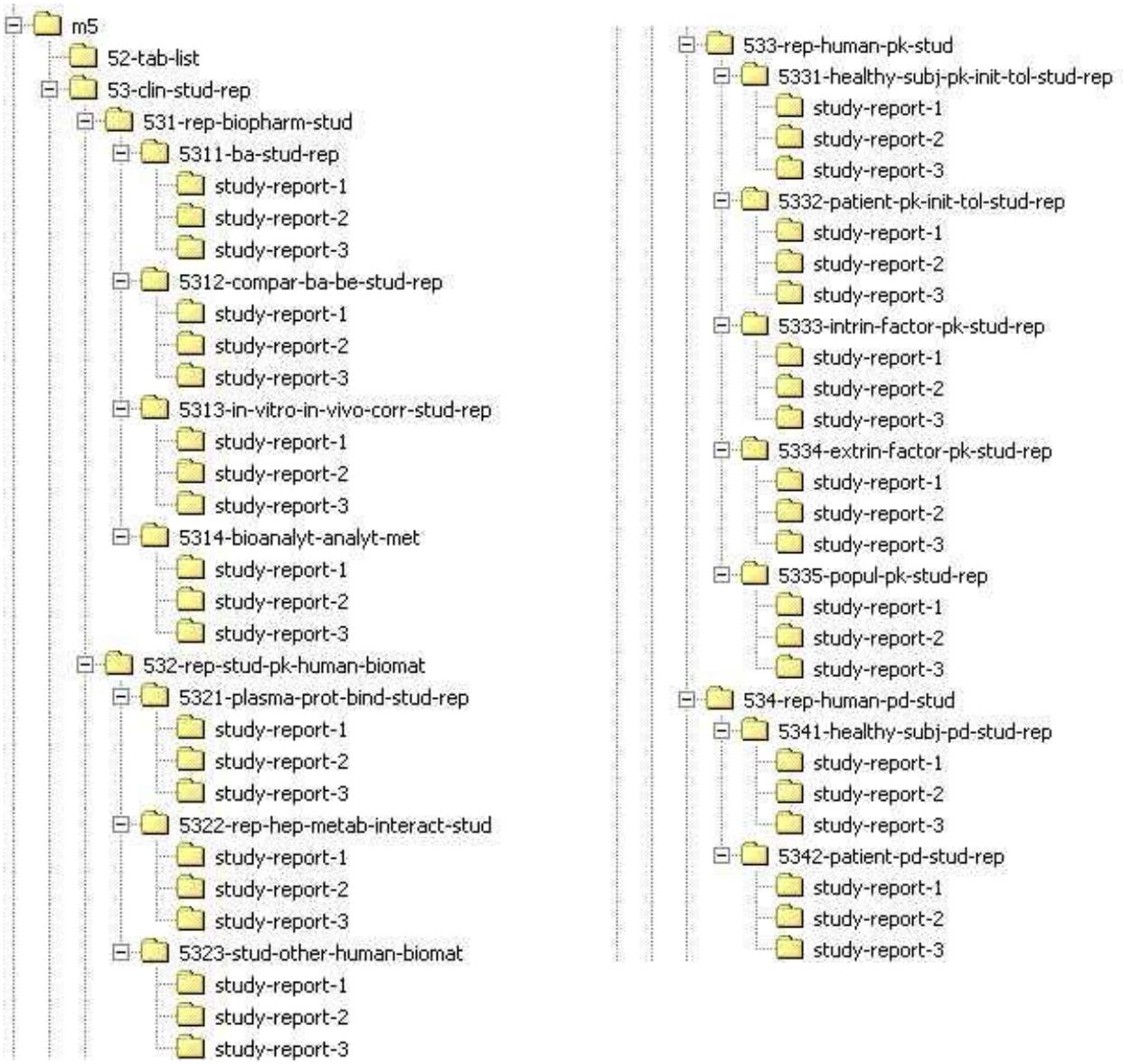


Figure 7: Module 5 Folder Structure

The CTD organization provides locations for case report forms and individual patient data listings inModule 5.3.7 and for literature references in Module 5.4.

In the eCTD, files for publications and literature references are located in the folder for Module 5.4. However, in the index.xml file the leaf elements for these publications and literature references are included under the same heading as the other study report files with additional information included through use of the study tagging file, if applicable in that

region. In addition, a repeat of the leaf element are placed under the heading for 5.4 Literature References.

Case report forms, data sets and individual patient data listings are organized according to regional guidance.

## 4.3 eCTD Modules Implementation Data Stores

To implement data for the structures in 4.2 above, a repository for the meta data is required. The meta data is read from the XML Backbone into relational data tables. Required tables are as follows:

| | **Primary Table** | **Foreign Tables** |
|---|---|---|
| 1 | Product | generic_name (All API names seperated by the + sign) |
| 2 | Applicant (business entity) | application |
| 3 | generic_branded | |
| 4 | ingredients | strength |
| | | INN |
| | | Manufacturer |
| | | GMP |
| | | preferred_national_name |
| | | substance_list |
| | | synonyms |
| | | ingredient type |
| | | FPP |
| | | formulation |
| 5 | Formulation | |
| 6 | ingredient type (API or Excipient or any other type in the future) | |
| 7 | FPP | Manufacturers |
| | | Country of Origin details |
| 8 | preferred national name | |
| 9 | substance list | |
| 10 | synonyms | |
| 11 | country_of_origin (from the geomasterlist tables) | |
| 12 | Strength | |
| 13 | dosage | |
| 14 | Dosage Form | |
| 15 | Dosage Route | |

| | | |
|---|---|---|
| 16 | Pack Size | |
| 17 | Pack units | |
| 18 | primary container | |
| 19 | Visual Description | |
| 20 | product images | product images paths |
| 21 | Shelf_life | |
| 22 | Storage Conditions | |
| 23 | Classification | classification type |
| | | classes (self referencing) |
| 24 | Legal_category | |
| 25 | Origin details (country, Market Authorization Holder (MAH), MAH authoritiy, MAH details) | MAH Authority |
| 26 | Lab_Analysis (business_entities: add sub-tables suggested here to business entities) | lab |
| | | certification body (WHO prequalified, KEBS) |
| | | certification bodies (for institution certified by more than one institution e.g. WHO,ISO,KEBS) |
| 27 | Manufacturers (Business Entities, here the entity has a GMP unlike the college or retails.) | |
| 28 | GMP Details (for API, FPP) | |
| 29 | Product_xtics | |
| 30 | Fpp Clinical/bioequivalence studies batches | |
| 31 | fpp Stability studies batches | |
| 32 | fpp Validation/production scale batches | |
| 33 | Composition_Summary (bio_equivalence/per admin unit: this table has values that will be calculated by views) | |
| 34 | API (sustance) | general_info |
| | | Nomenclature |
| | | Structure |
| | | General Properties |
| | | Manufacturer |
| | | Manufacturing Process and controls |
| | | Material control |
| | | Critical steps and intermediates control |
| | | Manufacturing Process Validation |
| | | Manufacturing process evalution |
| | | API Characterization |
| | | control |
| | | reference standards/materials |
| | | container closure system |

| | | |
|---|---|---|
| | | stability |
| 35 | FPP (add to FPP table) | Description |
| | | Composition |
| | | FPP Pharmaceutical Development |
| | | FPP Excpients Control |
| | | FPP Control |
| | | FPP Reference standards |
| | | FPP Stability |
| | | API Details Summary |
| 36 | Excipients | Facilities and Equipment |
| | | Adventitious Agents Safety Evalution |
| | | Novel excipients |
| | | Appendices Summary |
| 37 | Appendices | |
| 38 | Non-Clinical Overview for new Entities (sustance) | |
| 39 | Non-Clinical summaries for new Entities(sustance) | |
| 40 | Clinical Overview for new Entities | |
| 41 | Clinical Summary for new Entities | |
| 42 | Generics Clinical Overview and Summary | |
| 43 | Generics Product Development Rationale | |
| 44 | Generics Biopharmaceutics Studies | |
| 45 | Generics Summary of Biopharmaceutics Studies and Associated Analytical Methods | |
| 46 | Generics Overview and Summary of In VitroDissolution Tests complementary to Bioequivalence Studies | |
| 47 | Generics Overview and Summary of In VitroDissolution Tests in support of a Biowaiver | |
| 48 | Generics | Entities Clinical Studies Listing |
| | | Clinical Study Reports |
| | | Literature References |
| | | In Vitro dissolution tests complementary to Bioequivalence studies |
| | | in vitro dissolution test in support of bio-waiver |
| | | other clinical study data to support efficacy and safety of the product |
| | | Vet only Laboratory Animal Studies |
| | | Vet only Target Animal safety studies |
| | | Vet only Laboratory Animal Toxicity Studies |

| | | |
|---|---|---|
| | | Vet only Microbiological Safety Studies (for antimicrobial products) |
| 49 | New Chemical Entities | Entities Clinical Studies Listing |
| | | Clinical Study Reports |
| | | Literature References |
| | | In Vitro dissolution tests complementary to Bioequivalence studies |
| | | in vitro dissolution test in support of bio-waiver |
| | | other clinical study data to support efficacy and safety of the product |
| | | Vet only Laboratory Animal Studies |
| | | Vet only Target Animal safety studies |
| | | Vet only Laboratory Animal Toxicity Studies |
| | | Vet only Microbiological Safety Studies (for antimicrobial products) |

**Table 12: eCTD Data Stores**

## 4.4 Therapeutic Product Evaluation and Registration process

Therapeutic products are evaluated for registration following a basic process that involves submission of a fully filled form PPB 211 (eCTD) form, followed by a couple of steps towards product registration. Below is a table showing the steps:

| | Steps | Description | Actor |
|---|---|---|---|
| **1** | **Submit documents** | **Submit Application for registration of product Form PPB 211 (eCTD):**<br>**If applying**<br>**Note**<br>***Unsuccessful attempts at submission**<br>***Submission time**<br>**If not apply" go to confirm payment.** | **Applicant** |
| 2 | Validation | Validate the Application accordingly.<br>Confirm that all mandatory input fields are entered. Validate all data entered for consistency.<br>Confirm applicant is registered and has valid GMP certificate.<br>Confirm applicant has current valid license.<br>Generate an Application reference number and record application in the register<br>Acknowledge application | System |

| | | | |
|---|---|---|---|
| 3 | Invoice for evaluation | If chargeable service:<br>Generate invoice<br>Generate Request for Payment<br>If payment exempt service:<br>Update payment status to paid. | System |
| 4 | Confirm Payment | If invoiced, Confirm payment.<br>If not yet paid go to End process<br>If paid and selection is "Print" or "Acknowledge" go to housekeeping. | System |
| **5** | **Form team** | **Constitute evaluation team**<br>**Notify team members**<br>**Request for conflict of interest declaration** | **Registrar** |
| **6** | **confirmation** | **Confirm no conflict of interest** | **Team** |
| **7** | **Review** | **Determine if Lab analysis is required and move to 8 else move 10.** | **Team** |
| **8** | **Sample submission** | **Submit Laboratory Requisition Form, Submit to the Lab and Confirm the Lab reference no.**<br>**Confirm Receipt of certificate and Invoice** | **Team** |
| 9 | Lab result | Notify client and request for payment | System |
| 10 | Invoice for lab test | If chargeable service:<br>Generate invoice<br>Generate Request for Payment<br>If payment exempt service:<br>Update payment status to paid. | System |
| 11 | Confirm Payment | If invoiced, Confirm payment.<br>If not yet paid go to End process<br>If paid and selection is "Print" or "Acknowledge" go to housekeeping. | System |
| **12** | **Evaluation** | **Review the Dossier, and approve/reject**<br>Prepare report for Board Committee<br>Forward report to board committee | **Board** |
| **13** | **Approval** | **Review report and approve/reject** | **Board PC** |
| 14 | License | If approved, Generate certificate<br>Notify applicant | System |
| **15** | **Confirm Gazettiment** | **Gazette the Product** | **Registrar** |
| **16** | **Confirm** | **Confirm receipt of license** | **Applicant** |
| 17 | Housekeeping | If Action is "Print" print the filled form.<br>If Action is "Acknowledge" record end time. | System |
| 18 | End process | If Action is "Apply" Note completion time.<br>Exit the process. | System |

**Table 13: Product Registration Process. Blue is for Human External Client, Red is Human Internal Staff and Black is for System.**

Product Registration Data Flow Diagram – Process Numbered 2.1.1 - APPENDIX 4 – PPB Processes Numbering Convention

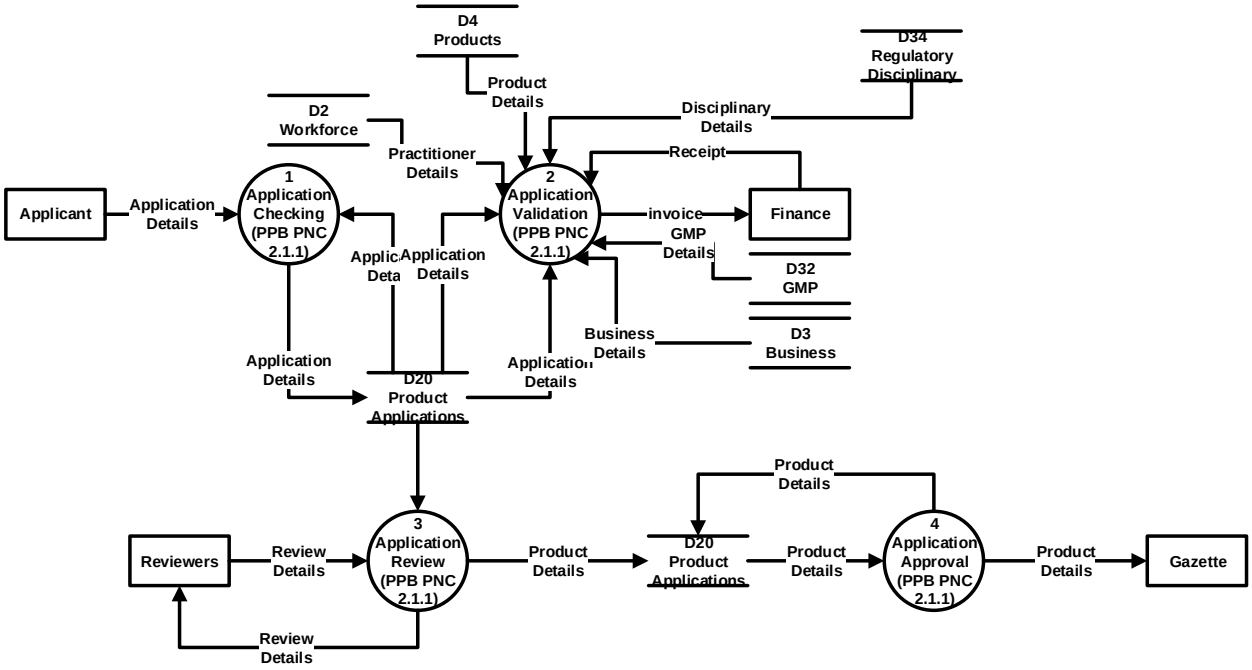


**Figure 8: Product Registration - Note the use of ICH M8 and PPB CTD**

These are bottom level processes for Product Registration process that is numbered 2.1.1 numbered in order of execution using PPB numbering convention:APPENDIX 4 – PPB Processes Numbering Convention. GMP is the abbreviation for Good Manufacturing Practices (GMP).

From Table 13 it is evident that clinical trials data is submitted as part of the eCTD documents and not separate data. In the data flow diagram Figure 8 there is no link to clinical trials data stores or process.

## 4.4 Clinical Trial Registry (CTR)

Clinical Trial Registry is Pharmacy and Poisons Board implementation of the SDTM by CDISC.

### *4.4.1 SDTM (source CDISC SDTM Implementation Guide (SDS Version 3.1)*

The SDTM standard provides a general framework for describing the information collected during studies and submitted to regulatory authorities. It is built around the concept of observations, which consist of discrete items of information collected during a study. Observations normally are storedas rows in a dataset. A group of observations on a topic is considered a domain.

Each observation is described by a series of variables. Each variable, which normally corresponds to a column in a dataset, can be classified according to its Role. A Role describes the type of information conveyed by the variable about each distinct observation and how it can be used. SDTM variables can be classified into five major roles:

1. Identifier variables - identify the study, the subject (individual human or animal or group of individuals) involved in the study, the domain, and the sequence number of the record.
2. Topic variables - specify the focus of the observation (such as the name of a lab test).
3. Timing variables - describe the timing of an observation (such as start date and end date).
4. Qualifier variables - include additional illustrative text, or numeric values that describe the results or additional traits of the observation (such as units or descriptive adjectives).
5. Rule variables, which express an algorithm or executable method to define start, end, or looping conditions in the Trial Design model.

The set of Qualifier variables can be further categorized into five sub-classes:

1. Grouping Qualifiers are used to group together a collection of observations within the same domain. Examples include --CAT and --SCAT.
2. Result Qualifiers describe the specific results associated with the topic variable in a Findings dataset. They answer the question raised by the topic variable. Result Qualifiers are --ORRES, --STRESC, and --STRESN.
3. Synonym Qualifiers specify an alternative name for a particular variable in an observation. Examples include --MODIFY and --DECOD, which are equivalent terms for a --TRT or --TERM Topic variable, and --TEST for --TESTCD.
4. Record Qualifiers define additional attributes of the observation record as a whole (rather than describing a particular variable within a record). Examples include --REASND, AESLIFE, and all other SAE flag variables in the AE domain; AGE, SEX, and RACE in the DM domain; and --BLFL, --POS, --LOC, --SPEC, and --NAM in a Findings domain
5. Variable Qualifiers are used to further modify or describe a specific variable within an observation and are only meaningful in the context of the variable they qualify.

Examples include --ORRESU, --ORNRHI, and --ORNRLO, all of which are Variable Qualifiers of --ORRES; and --DOSU, which is a Variable Qualifier of --DOSE.

For example, in the observation, “Subject 101 had mild nausea starting on Study Day 6”, the Topic variable value is the term for the adverse event, “NAUSEA”. The Identifier variable is the subject identifier, “101”. The Timing variable is the study day of the start of the event, which captures the information, “starting on Study Day 6”, while an example of a Record Qualifier is the severity, the value for which is “MILD”. Additional Timing and Qualifier variables could be included to provide the necessary detail to adequately describe an observation.

Most of the data collected in a study is about the subjects who are enrolled in the study. Sometimes, however, data is collected about other persons (Associated Persons, APs) who can be associated with the study, a particular study subject, or a device used in the study. Associated Persons may or may not have a familial relationship to a study subject.

Observations about study subjects are normally collected for all subjects in a series of domains. A domain is defined as a collection of logically related observations with a common topic. The logic of the relationship may pertain to the scientific subject matter of the data or to its role in the trial. Each domain dataset is distinguished by a unique, two-character code that should be used consistently throughout the submission. This code, which is stored in the SDTM variable named DOMAIN, is used in four ways: as the dataset name, the value of the DOMAIN variable in that dataset, as a prefix for most variable names in that dataset, and as a value in the RDOMAIN variable in relationship tables.

| **CDISC SDTM DOMAINS CLASS** | **DOMAIN NAME** | **DOMAIN DESCRIPTION** |
|---|---|---|
| Special Purpose | DM | Demographics |
| | CO | Comments |
| Interventions | CM | Concomitant Medications |
| | EX | Exposure |
| | SU | Substance Use |
| Events | AE | Adverse Events |
| | DS | Disposition |
| | DV | Protocol Deviations |

| | | |
|---|---|---|
| | MH | Medical History |
| Findings | DA | Drug Accountability |
| | EG | ECG |
| | IE | Inclusion / Exclusion Criteria Exceptions |
| | LB | Laboratory Results |
| | MB | Microbiology Specimens |
| | MS | Microbiology Susceptibility |
| | PC | Pharmacokinetic Concentrations |
| | PP | Pharmacokinetic Parameters |
| | PE | Physical Exam |
| | QS | Questionnaires |
| | SC | Subject Characteristics |
| | VS | Vital Signs |
| Trial Design | TE | Trial Elements |
| | TA | Trial Arms |
| | TV | Trial Visits |
| | SE | Subject Elements |
| | SV | Subject Visits |
| | TI | Trial Inclusion/Exclusion Criteria |
| | TS | Trial Summary |
| Relationship Data Sets | SUPPQUAL | Supplemental Qualifiers |
| | RELREC | Relate Records |

**Table 14: SDTM Domains**

All datasets are structured as flat files with rows representing observations and columns representing variables. Each dataset is described by metadata definitions that provide information about the variables used in the dataset. The metadata are described in a data definition document named “define” that is submitted with the data to regulatory authorities. (See the Case Report Tabulation Data Definition Specification [Define-XML], available at www.CDISC.org). Define-XML specifies seven distinct metadata attributes to describe SDTM data:

1. The Variable Name (limited to 8 characters)
2. A descriptive Variable Label, using up to 40 characters, which should be unique for each variable in the dataset
3. The data Type (e.g., whether the variable value is a character or numeric)
4. The set of controlled terminology for the value or the presentation format of the variable (Controlled Terms or Format)

5. The Origin of each variable
6. The Role of the variable, which determines how the variable is used in the dataset. Roles include Identifiers, Topic, Timing, and the five types of Qualifiers.
7. Comments or other relevant information about the variable or its data included by the sponsor as necessary to communicate information about the variable or its contents to a regulatory agency.

Data stored in these variables include both raw (as captured by the data provider) and derived values (e.g., converted into standard units or computed, such as age). The SDTM describes the name, label, role, and type for the standard variables. The origin attribute has controlled terminology defined by CDISC as do values for many of the SDTM variables.

When creating submissions, a sponsor may drop certain variables (those defined as permissible in the implementation guide) from the dataset and the corresponding descriptions from the Define-XML, as long as no data was collected for these variables. New sponsor defined variables cannot be added, and existing variables cannot be renamed or modified for novel usage(Clinical Data Interchange Standards Consortium, 2013).

### *4.4.1 SDTM Structure*

#### 4.4.1.1 CDISC SDTM Fundamental

CDISC SDTM's fundamental model for organizing clinical data

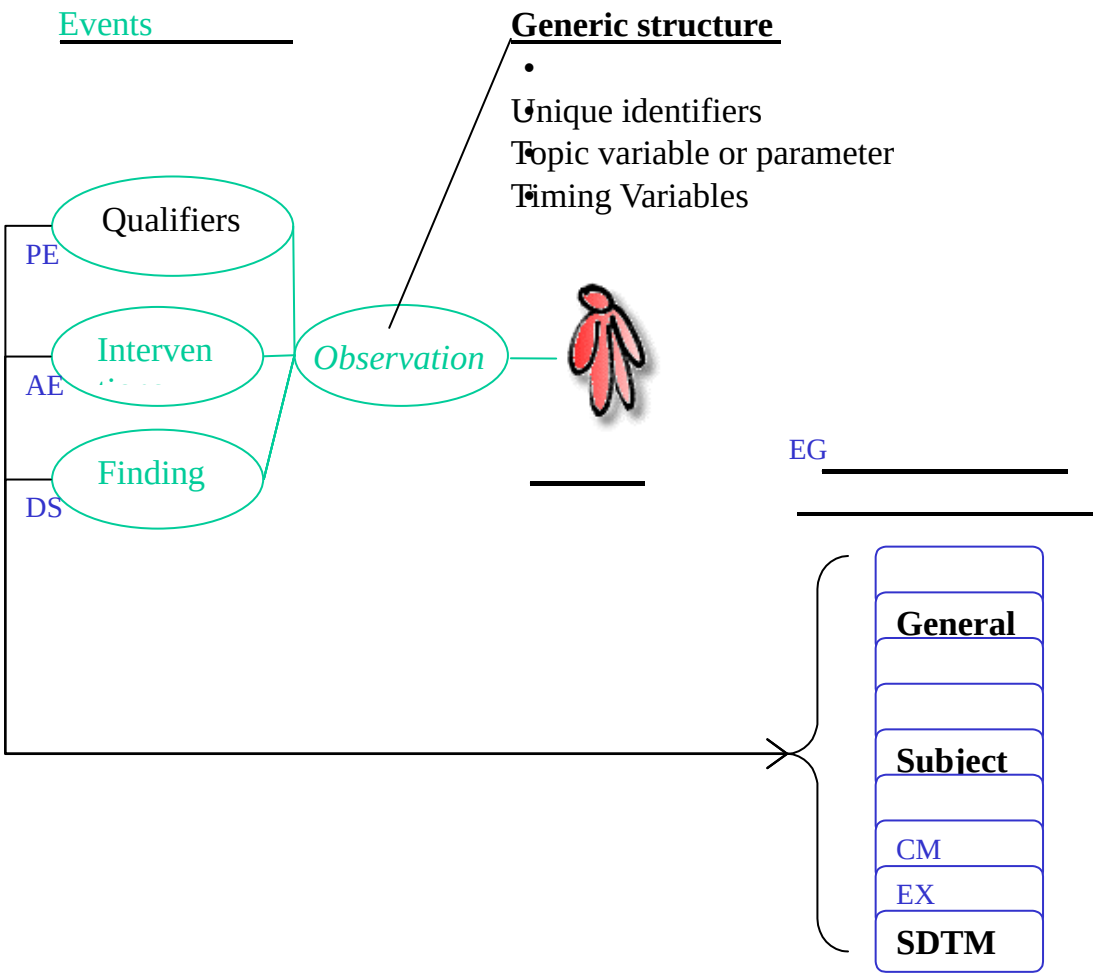


**Figure 9: SDTM Model with the trial subject.**

The patient/subject focused information model of the clinical 'reality' (general classes of observations on subjects: interventions, findings, events). This model has been developed by CDISC/SDS team and exist today only as text description (Clinical Data Interchange Standards Consortium, 2013).

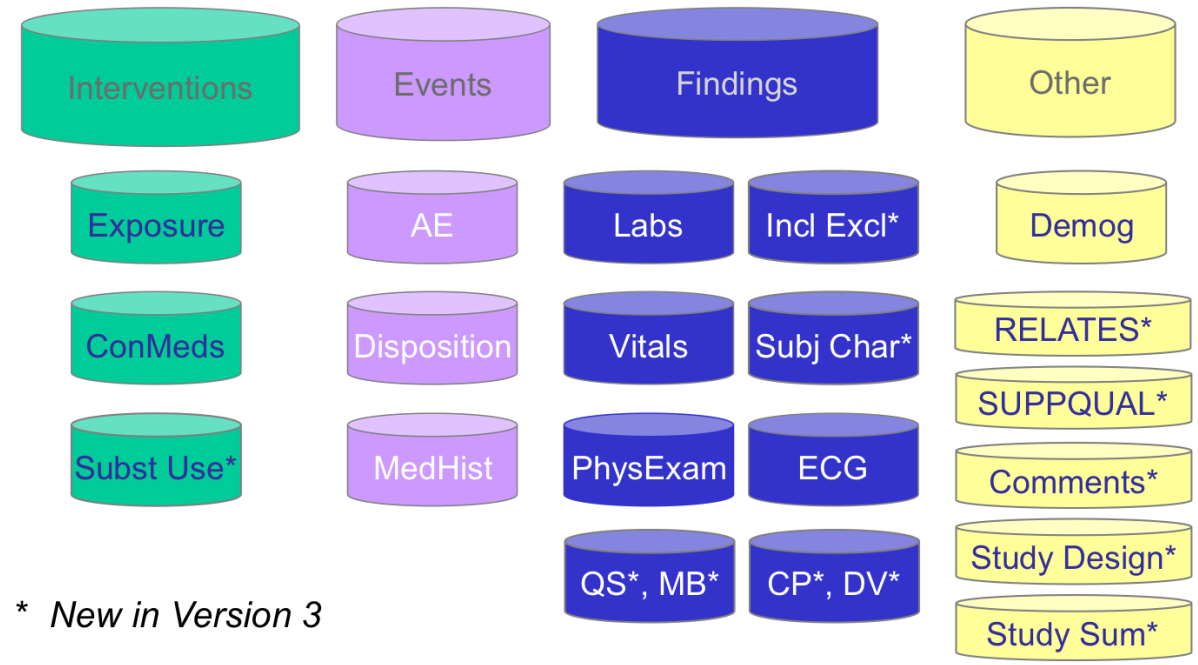


**Figure 10: SDTM Model with Version 3 elements.(Godoym, 2004)**

NB: Pharmacy and Poisons BoardClinical Trials Registry which is derived from the SDTM only covers the first role, Identifier Variables.

#### 4.4.1.2 Organisation of Data

CDISC SDTM fundamental model for organizing data collected in clinical trials Concept of Observations, which consist of discrete pieces of information collected during a study described by a series of named variables.

**General Classes of Observations: Events, Findings, Interventions**

Variable Roles: determines the type of information conveyed by the variable about each distinct observation: Topic variables, Identifier variables, Timing variables, Rule variables, and Qualifiers (Grouping, Result, Synonym, Record, Variable)

General principles and standards

| | STUDYID | DOMAIN | USUBJID | VSSEQ | VSTESTCD | VSTEST | VSPOS | VSLOC | VSORRES | VSORRESU | VSSTRESC |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Row 1** | ABC | VS | ABC-001-001 | 1 | SYSBP | Systolic Blood Pressure | SITTING | LEFT ARM | 154 | mmHg | 154 |
| **Row 2** | ABC | VS | ABC-001-001 | 2 | SYSBP | Systolic Blood Pressure | SITTING | LEFT ARM | 152 | mmHg | 152 |
| **Row 3** | ABC | VS | ABC-001-001 | 3 | SYSBP | Systolic Blood Pressure | SITTING | LEFT ARM | | | 153 |
| **Row 4** | ABC | VS | ABC-001-001 | 4 | DIABP | Diastolic Blood Pressure | SITTING | LEFT ARM | 44 | mmHg | 44 |
| **Row 5** | ABC | VS | ABC-001-001 | 5 | DIABP | Diastolic Blood Pressure | SITTING | LEFT ARM | 48 | mmHg | 48 |
| **Row 6** | ABC | VS | ABC-001-001 | 6 | DIABP | Diastolic Blood Pressure | SITTING | LEFT ARM | | | 46 |
| **Row 7** | ABC | VS | ABC-001-001 | 7 | PULSE | Pulse | SITTING | LEFT ARM | 72 | bpm | 72 |
| **Row 8** | ABC | VS | ABC-001-001 | 8 | TEMP | Temperature | | MOUTH | 34.7 | C | 34.7 |
| **Row 9** | ABC | VS | ABC-001-001 | 9 | TEMP | Temperature | | MOUTH | 36.2 | C | 36.2 |
| **Row 10** | ABC | VS | ABC-001-001 | 10 | WEIGHT | Weight | STANDING | | 90.5 | kg | 90.5 |
| **Row 11** | ABC | VS | ABC-001-001 | 11 | HEIGHT | Height | STANDING | | 157 | cm | 157 |
| **Row 12** | ABC | VS | ABC-001-001 | 12 | SYSBP | Systolic Blood Pressure | SITTING | LEFT ARM | 95 | mmHg | 95 |
| **Row 13** | ABC | VS | ABC-001-001 | 13 | DIABP | Diastolic Blood Pressure | SITTING | LEFT ARM | 44 | mmHg | 44 |
| **Row 14** | ABC | VS | ABC-001-001 | 14 | TEMP | Temperature | | MOUTH | 97.16 | F | 36.2 |
| **Row 15** | ABC | VS | ABC-001-001 | 15 | WEIGHT | Weight | | | | | |

| | VSSTRESN | VSSTRESU | VSSTAT | VSREASND | VSBLFL | VSDRVFL | VISIT | VISITNUM | VSTPT | VSTPTNUM | VISITDY |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Row 1 (cont)** | 154 | mmHg | | | | | BASELINE | 1 | BASELINE 1 | 1 | 1 |
| **Row 2 (cont)** | 152 | mmHg | | | | | BASELINE | 1 | BASELINE 2 | 2 | 1 |
| **Row 3 (cont)** | 153 | mmHg | | | Y | Y | BASELINE | 1 | | | 1 |
| **Row 4 (cont)** | 44 | mmHg | | | | | BASELINE | 1 | BASELINE 1 | 1 | 1 |
| **Row 5 (cont)** | 48 | mmHg | | | | | BASELINE | 1 | BASELINE 2 | 2 | 1 |
| **Row 6 (cont)** | 46 | mmHg | | | Y | Y | BASELINE | 1 | | | 1 |
| **Row 7 (cont)** | 72 | bpm | | | Y | | BASELINE | 1 | | | 1 |
| **Row 8 (cont)** | 34.7 | C | | | | | BASELINE | 1 | BASELINE 1 | 1 | 1 |
| **Row 9 (cont)** | 36.2 | C | | | Y | | BASELINE | 1 | BASELINE 2 | 2 | 1 |
| **Row 10 (cont)** | 90.5 | kg | | | Y | | BASELINE | 1 | | | 1 |
| **Row 11 (cont)** | 157 | cm | | | Y | | BASELINE | 1 | | | 1 |
| **Row 12 (cont)** | 95 | mmHg | | | | | VISIT 1 | 2 | | | 35 |
| **Row 13 (cont)** | 44 | mmHg | | | | | VISIT 1 | 2 | | | 35 |
| **Row 14 (cont)** | 36.2 | C | | | | | VISIT 1 | 2 | | | 35 |
| **Row 15 (cont)** | | | NOT DONE | Subject refused | | | VISIT 1 | 2 | | | 35 |

**Table 15: Data Sets of CDISC SDTM (VSSEQ are Record Identifiers and VSLOC is Textual interpretation of CODE from Code List)**

**Subclasses of Qualifiers**

- *Grouping Qualifiers* are used to group together a collection of observations within the same domain.
  - Examples include --CAT, --SCAT, --GRPID, --SPEC, --LOT, and --NAM. The latter three grouping qualifiers can be used to tie a set of observations to a common source (i.e., specimen, drug lot, or laboratory name, respectively).
- *Synonym Qualifiers* specify an alternative name for a particular variable in an observation.
  - Examples include --MODIFY and --DECOD, which are equivalent terms for a --TRT or --TERM topic variable, and --LOINC which is an equivalent term for a --TEST and --TESTCD.
- *Result Qualifiers* describe the specific results associated with the topic variable for a finding. It is the answer to the question raised by the topic variable.
  - Examples include --ORRES, --STRESC, and --STRESN.
- *Variable Qualifiers* are used to further modify or describe a specific variable within an observation and is only meaningful in the context of the variable they qualify.
  - Examples include --ORRESU, --ORNHI, and --ORNLO, all of which are variable qualifiers of --ORRES: and --DOSU, --DOSFRM, and --DOSFRQ, all of which are variable qualifiers of --DOSE. observation and is
- *Record Qualifiers* define additional attributes of the observation record as a whole (rather than describing a particular variable within a record).
  - Examples include --REASND, AESLIFE, and allother SAE flag variables in the AE domain; and --BLFL, --POS and --LOC.

**Variable Roles**

- **Topic variables**
  which specify the focus of the observation (such as the name of a lab test), and vary according to the type of observation.
- **Grouping qualifiers**
  are used to group together a collection of observations within the same domain.
  - Examples include --CAT, --SCAT, --GRPID, --SPEC, --LOT, and --NAM. The latter three grouping qualifiers can be used to tie a set of observations to a common source (i.e., specimen, drug lot, or laboratory name, respectively)
- **Synonym Qualifiers**
  specify an alternative name for a particular variable in an observation.
  - Examples include --MODIFY and --DECOD, which are equivalent terms for a --TRT or --TERM topic variable, and --LOINC which is an equivalent term for a --TEST and --TESTCD.

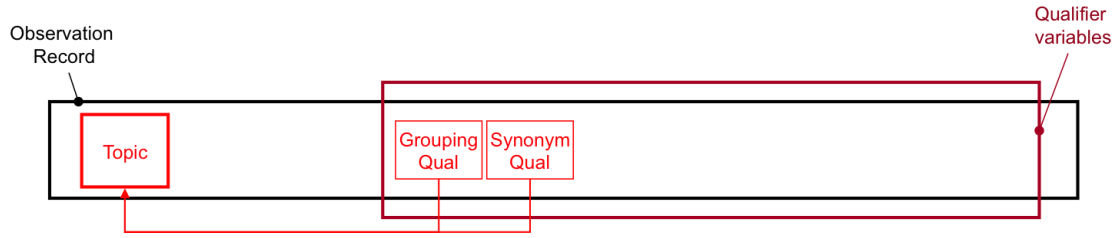


**Figure 11: SDTM Variable Roles**

- **Identifier variables**
  which identify the study, the subject (individual human or animal) involved in the study, the domain, and the sequence number of the record.
- **Timing variables**
  which describe the timing of an observation (such as start date and end date).
- **Result Qualifiers**
  describe the specific results associated with the topic variable for a finding. It is the answer to the question raised by the topic variable. Depending on the type of result (numeric or character) different variables are being used. Includes variables for both original (as supplied values) and for standardised values (for uniformity).
  - Examples include --ORRES, --STRESC, and --STRESN.

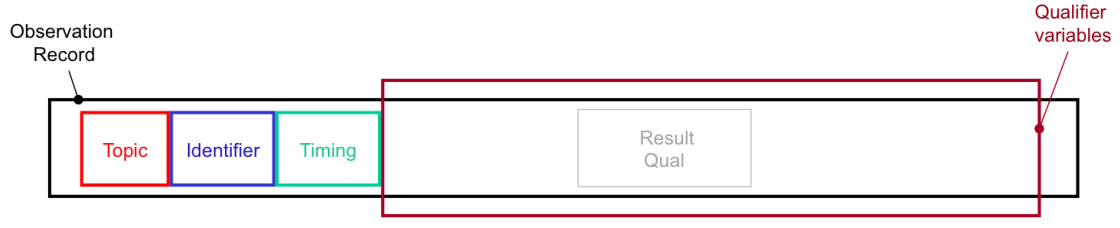


**Figure 12: Qualifier Variables**

- **Variable Qualifiers**
  are used to further modify or describe a specific variable within an observation and is only meaningful in the context of the variable they qualify.
  - Examples include --ORRESU, --ORNHI, and --ORNLO, all of which are variable qualifiers of --ORRES: and --DOSU, --DOSFRM, and --DOSFRQ, all of which are variable qualifiers of --DOSE.
  - Indictors where the results falls with respect to reference range

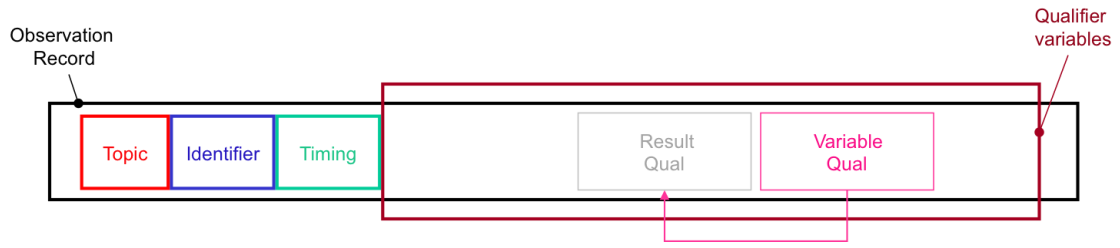


**Figure 13: Variable Qualifier**

- **Record Qualifiers**
  define additional attributes of the observation record as a whole (rather than describing a particular variable within a record).
  - Examples include --REASND, AESLIFE, and allother SAE flag variables in the AE domain; and
    --BLFL, --POS and --LOC.

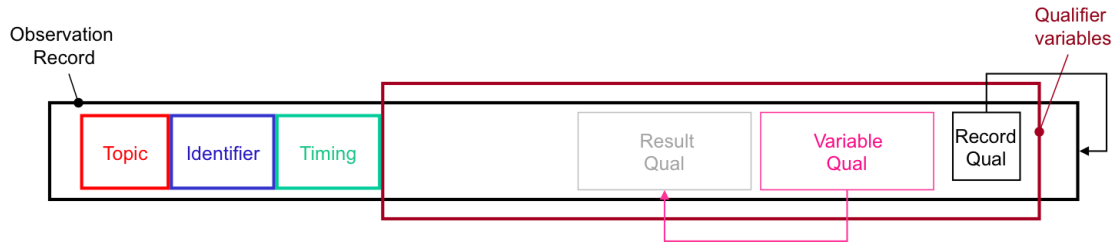


**Figure 14: Record Qualifiers**

- Topic variables
- Identifier variables
- Timing variables
- Rule variables
- Qualifier variables
  - Grouping Qualifiers
  - Result Qualifiers
  - Synonym Qualifiers
  - Record Qualifiers
  - Variable Qualifiers

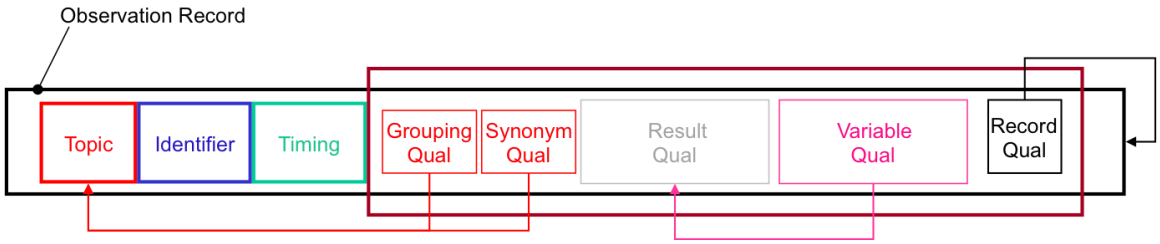


**Figure 15: SDTM Variables**

#### 4.4.1.4 Pharmacy and Poisons Board Identifier Capturing

Identifier Variables only cover the identity of the study, the subject (individual human or animal or group of individuals) involved in the study, the domain, and the sequence number of the record. These variables can be captured in accordance to the needs of the regulatory body involved. At the Pharmacy and Poisons Board they are captured as follows:

**Clinical Trials Application Form (PPB Form 221)**

**1. TYPE OF APPLICATION**

New Registration ☐ Review ☐ Extension ☐ Monitoring ☐ Termination ☐

**2. PARTICULARS OF PRINCIPAL INVESTIGATOR**

Title Mr. ( ) Mrs. ( ) Miss ( ) Dr ( ) Prof. ( ) Ms.

Surname……

…….Other

names……

……

Gender (M/F)……Date of Birth…….

ID/Passport No……Nationality…… Work Permit No/Alien ID……

Country of birth……Country of permanent residence……

County/State …… Constituency……

District…… Ward……

Post office

Box……..Code..……Town……

……

**Telephone Numbers**

Work Tel No…….

Mobile……Home…….

Fax no……E-

mail...……

**3. PROFESSIONAL DETAILS OF PI**

Profession of PI……..……

Professional Association……Membership

No……..

Highest Qualification……. Institution of

Award……..

Name of qualification……

Present position Held……..

**4. INSTITUTIONAL DETAILS OF PI**

Name of

Institution……

…….….

Physical Address ……(GPS)

Post office

Box……..Code..……

…….……

Telephone……..…….Fax……..…….E-

mail...……

PI Number**.....**

Study Title:
Protocol No:
Version No: Date of Protocol:
Study Drug:
ECCT Ref number (if applicable):
Sponsor:
Contact Person:
Address:
Telephone Number: Fax Number:
Cell Number: E-mail address:

1. **SITE DETAILS**

5.1 Number of Sites…….

| Country | Regulatory authority | Site Name | Site Coordinator (Name, qualification and address) | Number of key site staff | No. of trial Participants | Age Span of trial participants | Does this trial have a data monitoring committee? yes □ no □ |
|---|---|---|---|---|---|---|---|
| | | | | | | | |

5.2 Capacity of Kenyan Site(s):

**Site Name……**

| Name key staff | f u li ic tions o key staff | Experience in years | Accessible site facilities eg lab, ortu ry | emergency facilities | other relevant infrastructure |
|---|---|---|---|---|---|
| | | | | | |

## 2. DESIGN OF THE TRIAL

6.1 Is the trial Controlled? Yes No

6.1.1 **If controlled, specify the comparator:**

**Other medicinal product(s) □ Placebo□ Other □**
(specify)……..

**If placebo provide the following information**

| **Pharmaceutical for a ini tration** | **oute f** | **Composition, apart from the active substance(s):** | **If not identical to the IMP, specify major ingredients of t e pl cebo** |
|---|---|---|---|
| | | | |

6.2 Sampling Method? Random Non Random

6.3 Testing Approach

Open□ Single Blind□ Double Blind□ Parallel□
Crossover□
Other □ (Specify)……

**2.0 GROUP OF TRIAL SUBJECTS**

6.1 Type of trial subject

Healthy Volunteer □ Patients□ Specific Vulnerable Populations□

6.2 If Specific Vulnerable Populations,

Women of child bearing potential
Women of child bearing potential using contraception
Pregnant women
Nursing women
Emergency situation
Others

1.3 Are there subjects in the specified category incapable of giving consent?

Yes No

1.3.1 If yes Specify the number……

**1.4 Gender of the subjects**

Number of Male Number of Female

**7.0 CLINICAL TRIALS DELEGATION**

**7.1 Has the sponsor transferred any of the trial related duties and functions to another organization(s)?** Yes No

7.2 if Yes

Organization Details Duty/Responsibility

**8.0 INCLUSION/ EXCLUSION CRITERIA**

**8.1PRINCIPAL INCLUSION CRITERIA**

**8.2PRINCIPAL EXCLUSION CRITERIA**

**9.0PRIMARY END POINT(S)**

**10.0 scope of the trial**

| | | |
|---|---|---|
| Diagnosis | | □ |
| Prophylaxis | □ | |
| Therapy | | □ |
| Safety | □ | |
| Efficacy | | □ |
| Pharmacokinetic | | □ |
| Pharmacodynamic | □ | |
| Bioequivalence | | □ |
| Dose Response | | □ |
| Pharmacogenetic | | □ |
| Pharmacogenomic | □ | |

Pharmacoeconomic □
Others □
If others, specify:

**11.0 TRIAL PHASE**

11.1 Human pharmacology (Phase I) □
11.1.1 Is it:
First administration to humans □
Bioequivalence study □
Other : □
If other, please specify
11.2 Therapeutic exploratory (Phase II) □
11.3 Therapeutic confirmatory (Phase III) □
11.4 Therapeutic use(Phase IV)

12.0 OTHER DETAILS

12.1 Does the study have an indemnity cover Yes No
If Yes, Name of the insurer ……policy number …….
Expiry date…….

12.2 Does the study have a favourable opinion letter from recognized Institutional Review Board (IRB) and
Ethics committee? Yes No

If yes, approval date …….

12. 3 Does the study involve collaboration with any other institution(s) or regulatory authorities?
Yes No

12.4 If the trial is to be conducted in Kenya and not in the host country of the applicant / sponsor, provide an explanation:

12.5 Estimated duration of trial:

12.6 Name of other Regulatory Authorities to which applications to carry out this trial have been submitted, but approval has not yet been granted. Include date(s) of application:

**Table 16: Clinical Trials Form (Form 221)**

This means the Principal Investigator or the sponsoring institution has to submit the finding of a clinical trial in the format prescribed in the eCTD as that is the only regulatory format that Pharmacy and Poisons Board accepts any Clinical Trials Results. It also means the role

of the Pharmacy and Poisons Board in this case is just administrative supervisory as demonstrated in the Clinical Trials Processes and not technical evaluation of clinical trials during the clinical trials phase.

Additional to Form 221 the Principal Investigator shall attach a prescribe SDTM submission checklist showing the domains for which submission has been done.

Here is a sample from FDA of USA Table 17: FDA Sample SDTM submission Checklist.

| **STUDY ID:** | | **TITLE:** | |
|---|---|---|---|
| **TYPE** | **DOMAIN** | **Select Domains to be Submitted (X)** | **COMMENTS** |
| Trial Design | | | |
| | TA | ☐ | |
| | TE | ☐ | |
| | TI | ☐ | |
| | TS | ☐ | |
| | TV | ☐ | |
| Special Purpose | | | |
| | CO | ☐ | |
| | DM | ☒ | |
| | SE | ☐ | |
| | SV | ☐ | |
| Interventions | | | |
| | CM | ☒ | |
| | EX | ☒ | |
| | SU | ☐ | |
| Events | | | |
| | AE | ☒ | |
| | CE | ☐ | |
| | DS | ☒ | |
| | DV | ☐ | |
| | MH | ☐ | |
| Findings | | | |
| | DA | ☐ | |
| | EG | ☐ | |
| | IE | ☐ | |
| | LB | ☐ | |
| | MB | ☐ | |
| | MS | ☐ | |
| | PC | ☐ | |
| | PE | ☐ | |
| | PP | ☐ | |
| | QS | ☐ | |
| | SC | ☐ | |
| | VS | ☐ | |
| Findings About | | | |
| | FA | ☐ | |
| Relationships | | | |
| | RELREC | ☐ | |

| | | | |
|---|---|---|---|
| | SUPPQUAL | ☒ | |
| Custom | | | |
| | | ☐ | When creating customized domains, there are rules that need to be followed. For examples, please visit http://www.cdisc.org/sdtm, page 20 of SDTMIG 3.1.3 section 3.2.2 CONFORMANCE |
| | | ☐ | Spell out the acronyms |

**Table 17: FDA Sample SDTM submission Checklist.**

Clinical Trial Reviewers and the Principal Investigator settle on

1. The domains identified for the clinical trial study
2. Variables placed in the SUPPQUAL domain or multiple SUPP – domains
3. Any custom domains created by the Principal Investigator
4. Reviewers will ensure there are no other existing domains to place the variables that are in the SUPPQUAL domain or multiple SUPP – domains

### *4.4.2 Clinical Trials Processes*

| | Steps | Description | Actor |
|---|---|---|---|
| **1** | **Submit documents** | **If applying or extending submit Application for registration of clinical trials Form PPB221:**<br>**Note *Unsuccessful attempts at submission**<br>***Submission time**<br>**If not applying or extending go to confirm payment.** | **Applicant** |
| 2 | Check requirements | • Confirm that all mandatory input fields are entered. Validate all data entered for consistency.<br>• Confirm that the clinical trial has been approved by the Protocol committee<br>• Generate an application number<br>• Enter the application in the register | System |
| 3 | Invoice | If chargeable service:<br>• Generate invoice<br>• Generate Request for Payment<br>If payment exempt service:<br>Update payment status to paid. | System |
| 4 | Confirm Payment | If invoiced, Confirm payment.<br>If not yet paid go to End process<br>If paid and selection is "Print" or "Acknowledge" go to housekeeping. | System |
| **5** | **Assessment** | **Review the application and approve/reject** | **Board** |
| 6 | Notification | Notify the applicant of Approval/rejection | System |
| **7** | **Reporting** | **Report on Clinical Trial Progress** | **Applicant** |
| **8** | **Monitoring** | **Monitor Clinical Trial Progress** | **Board** |

| 9 | Termination | Stop Clinical Trial | Board |
|---|---|---|---|
| 11 | Housekeeping | If Action is “Print” print the filled form.<br>If Action is “Acknowledge” record end time. | System |
| 12 | End process | If Action is “Apply” Note completion time.<br>Exit the process. | System |

**Table 18: Clinical Trials Processes**

Clinical Trials Data Flow – PPB Process 2.2.1 - APPENDIX 4 – PPB Processes Numbering Convention

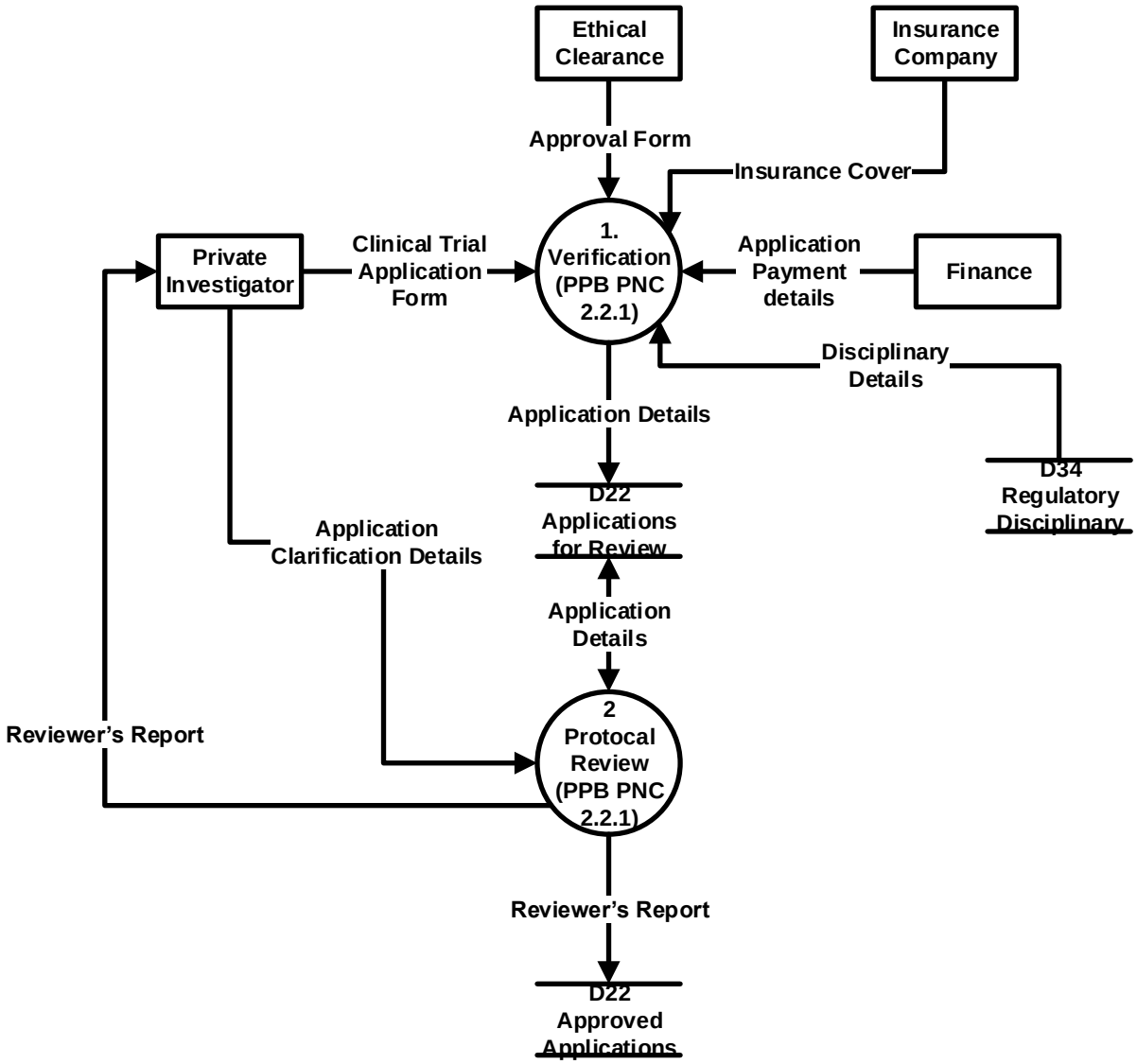


**Figure 16: Clinical Trials Data Flow**

From the processes steps as indicated in Table 18 and data flow diagramFigure 16, the Board is basically doing administrative supervision of clinical trials and the results of clinical trials are only received during product registration. The product of clinical trials process is to inform that the trial was done as per standards and requirements of SDTM but not reviewing the data of the process. After closure of clinical trials, there is not link to any other department which means data is just stored in CTR repository for future use or reference. The processes are numbered in order of execution following the PPB Processes Numbering Convention APPENDIX 4 – PPB Processes Numbering Convention

## 4.5 Capacity to Develop and Sustain eCTD and CTR Systems

E-Readiness survey was conducted in the EAC NMRAs to find and compare the readiness and capacity of NMRAs to develop, implement and sustain an eCTD system.NMRA visited were:

1. Departement De La Pharmacie, Du Medicament Et Des Laboratoires (DPML) Burundi
2. Rwanda Pharmacy Taskforce (RPT) Rwanda
3. National Drug Authority (NDA) Uganda
4. Pharmacy And Poisons Board (PPB) Kenya
5. Tanzania Food And Drug Authority (TFDA) Tanzania
6. Zanzibar Food And Drug Board (ZFDB) Zanzibar

The variables that were observed were as follows using the eReadiness questionnaire in APPENDIX 1 – EAC E-Readiness Assessment Tool and Capability Maturity Model in APPENDIX 2 – Capability Maturity Model:

Countries responded as follows:

**General Infrastructure and Operational Tools Status of Burundi**

| **Infrastructure** | **Observation** |
|---|---|
| Local Area Network and WAN. | DPML has no Local Area Network installed. |
| Existence of Management Information system for Medicine Registration and Regulated products. | No Management information system for Medicine registration is in place. |
| Interoperability with other system. | There are no systems that can be integrated. |
| Working Tools (Computer, Laptops, Printers, Scanners). | DPML has no Computers and associated accessories. |
| **Hosting** | **Observation** |
| Internet and bandwidth. | There is no Internet |
| **Security** | **Observation** |
| Internet Security Measures. | No internet security measures are in place. |
| Data centre and disaster recovery. | There is no data center and no disaster recovery site or plan. |
| **Processes** | **Observation** |
| ICT Policy, ICT Strategy and implementation Plan. | There is no ICT Policy, no strategy and implementation plan. |
| Internal Processes | There are no defined processes for the regulatory areas. |
| | |

| Sustainability | Observation |
|---|---|
| ICT User support and capacity building. | DPML has no IT personnel |
| Staffing and operation. | Inadequate staff in all areas both. |
| Professional ICT Security expert. | No ICT security expert |
| Training. | Needed basic training in all areas |

Table 19: DPML General infrastructure and operational tools status

Capability Maturity of Burundi

| Respondent Background | Respondent's Feedback |
|---|---|
| Position in organization of the respondent(s). **(1. Project Or Team Leader Manager, 2. Technical Member Software Engineering Process, 3. Group (Sepg) Member And 4. Other)** | Acting Head DPML |
| Areas respondent(s) are currently working in. **(1. Software Requirements, 2. Software Quality Assurance, 3. Software Design, 4. Configuration Management, 5. Code And Unit Test, 6. Software Process Improvement, 7. Test And Integration, 8. Other)** | None of the Areas |
| Have respondent(s) received any CMM training | None |
| Software past experience | No past assessment - Experience |
| Previous software assessment experience. | None |
| | |
| Noted systems the respondent(s) has had a chance to interact. | DPML participating in implementing LMIS (Logistics Information Management System) currently in two Districts. |
| | |
| **Does the respondent(s) have experience in the following areas:** | **Status** |
| Requirements Management | None |
| Software Project Planning | None |
| Software Project Tracking and Oversight | None |
| Software Subcontract Management | Yes |
| Software Quality Assurance | None |
| Software Configuration Management | None |
| Organization Process Focus | None |
| Organization Process Definition | None |
| Training Program | Yes |
| Integrated Software Management | None |
| Software Product Engineering | None |
| Intergroup Coordination | None |
| Peer Reviews | None |
| Quantitative Process Management | None |
| Software Quality Management | None |

| | |
|---|---|
| Defect Prevention | None |
| Technology Change Management | None |
| Process Change Management | None |

Table 20: DPML Capability Maturity

General Infrastructure and Operational Tools Status of Rwanda

| **Infrastructure** | **Observation** |
|---|---|
| Local Area Network and WAN | Local area Network is available. |
| Existence of Management Information system for Medicine Registration and Regulated products | No Management Information system for Medicine registration and regulated products is available. |
| Interoperability with other system | No systems for interoperability. |
| Working Tools (Computer, Laptops, Printers, Scanners) | There are adequate working tools, computers, Laptops and printers for existing staff |
| **Hosting** | **Observation** |
| Internet and bandwidth | Internet is available. By law each government building must be connected to internet. |
| **Security** | **Observation** |
| Internet Security Measures | There are no security measures for RPT and the security measures available are for MoH |
| Data center and disaster recovery | RPT does not have its own server room or data centre and intends to host its data at the National Data Center. |
| **Processes** | **Observation** |
| ICT Policy, ICT Strategy and implementation Plan | RPT is dependent on the Ministry for its ICT Policy, ICT Strategy and Implementation plan. |
| Internal Processes | Internal processes are<br>I Registration of Medicine<br>ii Licensing<br>iii Import and Export Management<br>iv Inspection |
| **Sustainability** | **Observation** |
| ICT User support and capacity building | RPT has not ICT personnel and is dependent on the ministry. |
| Staffing and operation | Inadequate staff |
| Professional ICT Security expert | There no ICT security expert |
| Training | Training is needed for industry certifications |

Table 21: RPT General Infrastructure and Operational Tools Status

Capability Maturity of Rwanda

| Respondent Background | Respondent's Feedback |
|---|---|
| | |
| Position in organisation of the respondent(s). **1. Project Or Team Leader Manager, 2. Technical Member Software Engineering Process, 3. Group (Sepg) Member And 4. Other** | Group |
| Areas respondent(s) are currently working in. **1. Software Requirements, 2. Software Quality Assurance, 3. Software Design, 4. Configuration Management, 5. Code And Unit Test, 6. Software Process Improvement, 7. Test And Integration, 8. Other** | All Areas |
| Have respondent(s) received any CMM training | None |
| Software past experience | 2 years Organization experience |
| Previous software assessment experience. | None |
| | |
| Noted systems the respondent(s) has had a chance to interact. | Laboratory Information Management System (LIMS) |
| | |
| **Does the respondent(s) have experience in the following areas:** | |
| Requirements Management | Yes |
| Software Project Planning | Yes |
| Software Project Tracking and Oversight | Yes |
| Software Subcontract Management | Yes |
| Software Quality Assurance | Yes |
| Software Configuration Management | Yes |
| Organization Process Focus | Yes |
| Organization Process Definition | Yes |
| Training Program | Yes |
| Integrated Software Management | Yes |
| Software Product Engineering | Yes |
| Intergroup Coordination | Yes |
| Peer Reviews | Yes |
| Quantitative Process Management | Yes |
| Software Quality Management | Yes |
| Defect Prevention | Yes |
| Technology Change Management | Yes |
| Process Change Management | Yes |

Table 22: RPT Capability Maturity

General Infrastructure and Operational Tools Status of Uganda

| Infrastructure | Observation |
|---|---|

| | |
|---|---|
| Local Area Network and WAN | There is well defined LAN and WAN |
| Existence of Management Information system for Medicine Registration and Regulated products | A stand alone Management Information system – DORA - exists. |
| Interoperability with other system | Existing systems need to be re-engineered so as to allow integration with other system |
| Working Tools (Computer, Laptops ,Printers, Scanners) | Adequate working tools for existing staff |
| **Hosting** | **Observation** |
| Internet and bandwidth | 4 Mbps bandwidth available |
| **Security** | **Observation** |
| Internet Security Measures | Firewall available |
| Data centre and disaster recovery | On premises data centre and data recovery site. |
| **Processes** | **Observation** |
| ICT Policy, ICT Strategy and implementation Plan | ICT Policy, ICT strategy and implementation plan available. |
| Internal Processes | Product registration<br>Trade facilitation<br>Enforcement |
| **Sustainability** | **Observation** |
| ICT User support and capacity building | There is no ICT personnel |
| Staffing and operation | Inadequate staff |
| Professional ICT Security expert | No ICT security expert available. |

Table 23: NDA General Infrastructure and Operational Tools Status

Capability Maturity of Uganda

| **Respondent Background** | **Respondent's Feedback** |
|---|---|
| | |
| Position in organisation of the respondent(s). **1. Project Or Team Leader Manager, 2. Technical Member Software Engineering Process, 3. Group (Sepg) Member And 4. Other** | Group |
| Areas respondent(s) are currently working in. **1. Software Requirements, 2. Software Quality Assurance, 3. Software Design, 4. Configuration Management, 5. Code And Unit Test, 6. Software Process Improvement, 7. Test And Integration, 8. Other** | Software Requirements, Design, Process Management, Test and Integration |
| Have respondent(s) received any CMM training | Done Via Skype |
| Software past experience | Organization 2 - 3 years |
| Previous software assessment experience. | Done Via Skype |
| | |

| | |
|---|---|
| Noted systems the respondent(s) has had a chance to interact. | LIMS - project stopped due to funding challenges. DORA |
| | |
| **Does the respondent(s) have experience in the following areas:** | |
| Requirements Management | Yes |
| Software Project Planning | Yes |
| Software Project Tracking and Oversight | Yes |
| Software Subcontract Management | Yes |
| Software Quality Assurance | Yes |
| Software Configuration Management | Yes |
| Organization Process Focus | Yes |
| Organization Process Definition | Yes |
| Training Program | Yes |
| Integrated Software Management | Yes |
| Software Product Engineering | Yes |
| Intergroup Coordination | Yes |
| Peer Reviews | Yes |
| Quantitative Process Management | Yes |
| Software Quality Management | Yes |
| Defect Prevention | Yes |
| Technology Change Management | Yes |
| Process Change Management | Yes |

Table 24: NDA Capability Maturity

General Infrastructure and Operational Tools Status of Kenya

| **Infrastructure** | **Observation** |
|---|---|
| Local Area Network and WAN | There is well defined LAN |
| Existence of Management Information system for Medicine Registration and Regulated products | There is Management Information system for medicine registrations and regulated. |
| Interoperability with other system | The system can be Integrated with other coming system |
| Working Tools (Computer, Laptops ,Printers, Scanners) | There are enough working tools for existing. |
| **Hosting** | **Observation** |
| Internet and bandwidth | 4 Mbps fiber internet. |
| **Security** | **Observation** |
| Internet Security Measures | There is Firewall as security measure |
| Data centre and disaster recovery | They have internal data center and there is no disaster recovery site |
| **Processes** | **Observation** |

| | |
|---|---|
| ICT Policy, ICT Strategy and implementation Plan | They have ICT Policy, ICT strategy and implementation plan |
| Internal Processes | Internal processes are<br>Pharmacy practice<br>Product registration<br>Trade facilitation<br>Enforcement |
| **Sustainability** | **Observation** |
| ICT User support and capacity building | There about 5 ICT personnel |
| Staffing and operation | There is inadequate staff |
| Professional ICT Security expert | There is no ICT security expert |

Table 25: PPB General infrastructure and operational tools status

Capability Maturity of Kenya

| **Respondent Background** | **Respondent's Feedback** |
|---|---|
| | |
| Position in organization of the respondent(s). **(1. PROJECT OR TEAM LEADER MANAGER, 2. TECHNICAL MEMBER SOFTWARE ENGINEERING PROCESS, 3. GROUP (SEPG) MEMBER and 4. OTHER)** | Group |
| Areas respondent(s) are currently working in. **(1. SOFTWARE REQUIREMENTS, 2. SOFTWARE QUALITY ASSURANCE, 3. SOFTWARE DESIGN, 4. CONFIGURATION MANAGEMENT, 5. CODE AND UNIT TEST, 6. SOFTWARE PROCESS IMPROVEMENT, 7. TEST AND INTEGRATION, 8. OTHER)** | All areas |
| Have respondent(s) received any CMM training | One CDC/Emory |
| Software past experience | 1.5 - 7 Years ICT Department |
| Previous software assessment experience. | None |
| | |
| Noted systems the respondent(s) has had a chance to interact. | E-Portal, PV, CTR, IMEX, Finance ABNO |
| | |
| **Does the respondent(s) have experience in the following areas:** | |
| Requirements Management | Yes |
| Software Project Planning | Yes |
| Software Project Tracking and Oversight | Yes |
| Software Subcontract Management | Yes |
| Software Quality Assurance | Yes |
| Software Configuration Management | Yes |
| Organization Process Focus | Yes |
| Organization Process Definition | Yes |

| | |
|---|---|
| Training Program | Yes |
| Integrated Software Management | Yes |
| Software Product Engineering | Yes |
| Intergroup Coordination | Yes |
| Peer Reviews | Yes |
| Quantitative Process Management | Yes |
| Software Quality Management | Yes |
| Defect Prevention | Yes |
| Technology Change Management | Yes |
| Process Change Management | Yes |

Table 26: PPB capability maturity

General Infrastructure and Operational Tools Status of Tanzania Mainland

| **Infrastructure** | **Observation** |
|---|---|
| Local Area Network and WAN | Well defined LAN. Currently there is no WAN |
| Existence of Management Information system for Medicine Registration and Regulated products | There is Management information system for medicine registration and other regulated products |
| Interoperability with other system | The system can be integrated with other system |
| Working Tools (Computer, Laptops ,Printers, Scanners) | Adequate working tools for Staff |
| **Hosting** | **Observation** |
| Internet and bandwidth | There is internet of 2mbps |
| **Security** | **Observation** |
| Internet Security Measures | There is Firewall as a security measure |
| Data centre and disaster recovery | They have internal data centre and disaster recovery site in one of their premises |
| **Processes** | **Observation** |
| ICT Policy, ICT Strategy and implementation Plan | They have ICT Policy, ICT strategy and implementation Plan |
| Internal Processes | Internal processes are<br>Registration of Medicine,Food,cosmetic,medical device<br>Importion and exportation of Medicine,Food,cosmetic and medical<br>GMP and Inspection<br>Licensing<br>Laboratory analysis for Medicine,Food,cosmetic and medical device |
| **Sustainability** | **Observation** |
| ICT User support and capacity building | There are 4 ICT personnel |
| Staffing and operation | Inadequate staff |
| Professional ICT Security expert | There is no ICT security expert |

**Table 27: TFDA General Infrastructure and operational tools status**

CAPABILITY MATURITY OF TANZANIA MAINLAND

| **Respondent Background** | **Respondent's Feedback** |
|---|---|
| | |
| Position in organization of the respondent(s). **(1. PROJECT OR TEAM LEADER MANAGER, 2. TECHNICAL MEMBER SOFTWARE ENGINEERING PROCESS, 3. GROUP (SEPG) MEMBER and 4. OTHER)** | Group |
| Areas respondent(s) are currently working in. **(1. SOFTWARE REQUIREMENTS, 2. SOFTWARE QUALITY ASSURANCE, 3. SOFTWARE DESIGN, 4. CONFIGURATION MANAGEMENT, 5. CODE AND UNIT TEST, 6. SOFTWARE PROCESS IMPROVEMENT, 7. TEST AND INTEGRATION, 8. OTHER)** | All areas |
| Have respondent(s) received any CMM training | Yes |
| Software past experience | 0.3 - 9 years Personnal and organisational |
| Previous software assessment experience. | Yes |
| | |
| Noted systems the respondent(s) has had a chance to interact. | IMS, e-portal, Finance EPICOR, |
| | |
| **Does the respondent(s) have experience in the following areas:** | |
| Requirements Management | Yes |
| Software Project Planning | Yes |
| Software Project Tracking and Oversight | Yes |
| Software Subcontract Management | Yes |
| Software Quality Assurance | Yes |
| Software Configuration Management | Yes |
| Organization Process Focus | Yes |
| Organization Process Definition | Yes |
| Training Program | Yes |
| Integrated Software Management | Yes |
| Software Product Engineering | Yes |
| Intergroup Coordination | Yes |
| Peer Reviews | Yes |
| Quantitative Process Management | Yes |
| Software Quality Management | Yes |
| Defect Prevention | Yes |
| Technology Change Management | Yes |
| Process Change Management | Yes |

**Table 28: TFDA Capability Maturity**

General Infrastructure and Operational Tools Status of Zanzibar

| **Infrastructure** | **Observation** |
|---|---|
| Local Area Network and WAN | There is no Local Area Network |
| Existence of Management Information system for Medicine Registration and Regulated products | There is no Management Information system for medicine registration and regulated products |
| Interoperability with other system | There is no system |
| Working Tools (Computer, Laptops, Printers, Scanners) | Inadequate working tools |
| **Hosting** | **Observation** |
| Internet and bandwidth | ISP Controlled connection |
| **Security** | **Observation** |
| Internet Security Measures | No security measures in place |
| Data centre and disaster recovery | There is no any data centre and disaster recovery |
| **Processes** | **Observation** |
| ICT Policy, ICT Strategy and implementation Plan | There is no ICT Policy ,ICT strategy and no implementation plan |
| Internal Processes | The internal processes are<br>Registration of Food, medicine and cosmetic<br>Importation of medicine<br>Licensing |
| **Sustainability** | **Observation** |
| ICT User support and capacity building | 2 ICT Officers |
| Staffing and operation | Inadequate staff |
| Professional ICT Security expert | There is no ICT security expert |

**Table 29: General Infrastructure and Operational Tools Status of Zanzibar**

Capability Maturity of Zanzibar

| **Respondent Background** | **Respondent's Feedback** |
|---|---|
| | |
| Position in organization of the respondent(s). **(1. PROJECT OR TEAM LEADER MANAGER, 2. TECHNICAL MEMBER SOFTWARE ENGINEERING PROCESS, 3. GROUP (SEPG) MEMBER and 4. OTHER)** | Group |

| | |
|---|---|
| Areas respondent(s) are currently working in. **(1. SOFTWARE REQUIREMENTS, 2. SOFTWARE QUALITY ASSURANCE, 3. SOFTWARE DESIGN, 4. CONFIGURATION MANAGEMENT, 5. CODE AND UNIT TEST, 6. SOFTWARE PROCESS IMPROVEMENT, 7. TEST AND INTEGRATION, 8. OTHER)** | ICT officers in all areas |
| Have respondent(s) received any CMM training | None |
| Software past experience | None (new ICT officers from college) |
| Previous software assessment experience. | None |
| | |
| Noted systems the respondent(s) has had a chance to interact. | None |
| | |
| **Does the respondent(s) have experience in the following areas:** | |
| Requirements Management | Yes |
| Software Project Planning | Yes |
| Software Project Tracking and Oversight | Yes |
| Software Subcontract Management | Yes |
| Software Quality Assurance | Yes |
| Software Configuration Management | Yes |
| Organization Process Focus | Yes |
| Organization Process Definition | Yes |
| Training Program | Yes |
| Integrated Software Management | Yes |
| Software Product Engineering | Yes |
| Intergroup Coordination | Yes |
| Peer Reviews | Yes |
| Quantitative Process Management | Yes |
| Software Quality Management | Yes |
| Defect Prevention | Yes |
| Technology Change Management | Yes |
| Process Change Management | Yes |

**Table 30: Capability Maturity**

### *4.5.1 Comparative Analysis of the EAC NMRA findings*

The first item that you will notice from the above responses is that Kenya is the only country with electronic systems for both eCTD and CTR, Tanzania and Uganda have eCTD but don't have CTR.

Another significant issue is the status of Burundi which indicates that DPML has no capacity to develop and implement any system.

Tanzania, Uganda and Kenya are the only countries with operation eCTD systems and therefore will set the standards for the other countries. With the support from development partners, Rwanda and Zanzibar are in a position to get to the same level as Tanzania, Uganda and Kenya, leaving Burundi as the only challenge area.

All NMRAs had well defined processes with the exception of Burundi.

### *4.5.2 Kenya's Position*

Based on the E-Readiness Survey conducted by the EAC, Kenya is capable of developing, implementing and sustaining an eCTD and CTR system. The finding also indicate that the systems implemented in Kenya meet the requirements of EAC and therefore will be adopted by other countries or used as a reference point taking into account they are similar to those in Tanzania and Uganda. It can therefore be concluded that the status quo in Kenya remains.

### *4.5.3EAC and Architecture Integration*

The E-Readiness points to the lack of clinical trials systems in the region.Kenya is the only country with a CTR system in the EAC. If integration of the data architectures is to be done, it can only be done in Kenya and may be difficult to do at the regional level. Integration of architectures in therapeutic products has not been tried before at a national level let alone a regional level. However based on the observations it will be very easy for the other EAC countries to copy and implement the Kenyan system once the same has been successfully done. This is because it has been shown that the countries in the EAC have the capacity to implement systems.

E-Readiness report also shows a very sad part of reality. The EAC countries don't have the advanced status of ICT like the western countries. It will be very difficult for any EAC country to implement systems at the level of FDA of USA and Swissmedic of Switzerland. As evidenced in the report, systems development is piecemeal, desperate and isolated. There is no coordinate approach to system development. What the countries exhibited was the capacity to develop systems and no major system to show. The systems demonstrated are not a reflection of the expected automation for NMRAs and are not commensurate to the capacity

indicated by the countries. Better and larger systems would be expected from organisations with the capacity implied by the countries.

# CHAPTER FIVE – PROPOSED SOLUTION

## 5.0 Introduction

This chapter explores the two architectures eCTD and CTR and gives the best possible way the two architectures can be integrated to benefit the regulation of therapeutic products. It also explains why data schema merging is not the best option and the benefits of architecture interfacing.

## 5.1 eCTD and CTR Architectures Integration

Unlike earlier perceptions, the implementation of CTR in Kenya is incomplete as per the CDISC SDTM standards. PPB has only implemented one role, Identifier Variables, which is the very basic item in the standard and will not need the implementation of Qualifier Variables Classes and Distinct Meta Data Variables.

eCTD captures Clinical Trials Reports in Module 4 and Module 5. In Module 4 Non-Clinical Studies Reports are captured. Non-Clinical trials are trials conducted on non humans, they could be whole animals or in vitro (latin for in glass, studies in experimental biology are those that are conducted using components of an organism that have been isolated from their usual biological surroundings in order to permit a more detailed or more convenient analysis than can be done with whole organisms). Module 5 captures Clinical Study Reports, that is studies done in humans. The reports in both Module 4 and Module 5 are generated by the Principal Investigator based on the data captured during clinical trials in the roles Identifier Variables, Topic Variables, Timing Variables, Qualifier Variables and Rule Variables of the SDTM architecture of CDISC.

Since eCTD requires Clinical Trials Reports, which are generated from analysis of data in all Roles, it therefore mean all that is required is a simple query to the CTR registry to validate that the clinical data presented is from a clinical trial that was done and supervised by the Board.

This however subjects the Board to huge data gaps.

1. It is not possible to validate clinical trials results since only administrative data is available.
2. Clinical Trials Reports have to be evaluated without the benefit of validating the original data.

## 5.2 eCTD and CTR Architectures Proposed Integration Approach

Full and proper integration of eCTD and CTR Architectures would follow five steps.

1. Review of Clinical Trials policy to entrench and enforce SDTM and other clinical trials standards as proposed by CDISC like Standard for Exchange of NonClinical Data (SEND) in the CTR architecture. Refer to 2.1 Legal and Electronic StandardsLimitations and Proposed Solution.
2. Review of Therapeutic Products Evaluation and Registration process and the Clinical Trials process to allow data flow between the two processes.
3. Full electronic implementation of SDTM standardin the CTR architecture as outlined out by CDISC.
4. Human capacity building.
5. Integration of the CDISC SDTM to eCTD using:
    a. formular to integrate the various items of SDTM to eCTD that is:

$$x = \sum_{m \in S} d(m)$$

    b. Submit CDISC SDTM data to eCTD modules 4 and 5 using predetermined hierachy.
    c. Store data in one repository with both eCTD and SDTM but with each architecure being distinct. This should allow for storage and retrieval using for each of the architectures as stipulated by each.

### *5.2.1 Step 1: Review of Clinical Trials Policy*

Currently the Board only registers and supervises clinical trials at the administrative level. The reasons being:

1. The legal framework needs to be changed to require the Board to explicitly regulate clinical trials. Refer to2.1 Legal and Electronic StandardsLimitations and Proposed Solution.
2. Lack of a firm research oriented market for clinical trials. Many products in Kenya are imported and the locally manufactured products are actually generics of products whose clinical trials were done in the West (Europe and America). This means the Board has to reduce the data burden in order to encourage clinical trials.

Despite the challenges listed, implementation of CDISC standards is still a requirement for the Board to implement and other methods of encouraging clinical trials should be explored. Legal issues can be addressed in order to strengthen the regulation of clinical trials.

### *5.2.2 Step 2: Processes Re-Engineering*

Therapeutic Products Evaluation and Registration processes and Clinical Trials processes need to be re-engineered to allow for data exchange. Currently products are registered based on the clinical trials reports and without any validation from clinical trials data. Exchange of data would mean that all clinical trials conducted in Kenya or outside Kenya must produce

data in SDTM standard for the CTR architecture and the same is reviewed by clinical trials experts to validate the reports presented to the eCTD module 4 and 5.

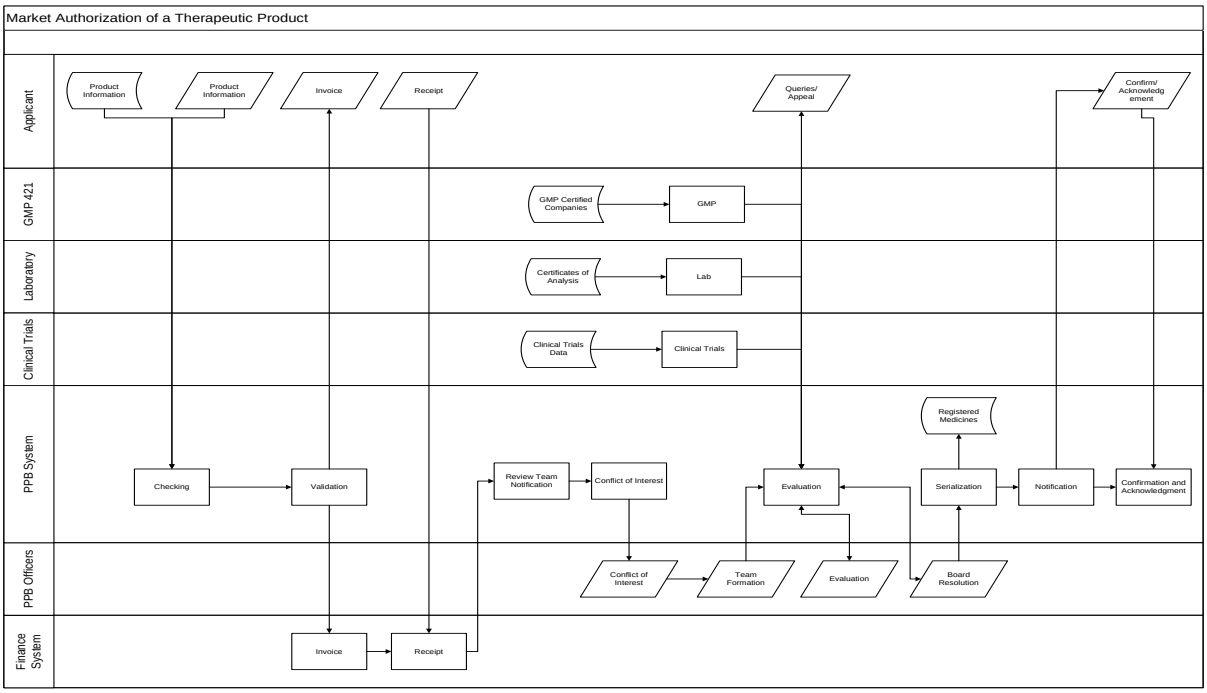


**Figure 17: New Re-Engineered Product Registration Process with Clinical Trials Input**

eCTD evaluation should be informed by data coming from CTR to validate the reports before registering a product as show in Figure 17: New Re-Engineered Product Registration Process with Clinical Trials Input.

The re-engineered drug registration process therefore would have the steps as shown in Table 31: Re-engineered Drug Registration Process

| | Steps | Description | Actor |
|---|---|---|---|
| **1** | **Submit documents** | **Submit Application for registration of product Form PPB 211 (eCTD):**<br>**If applying**<br>**Note**<br>***Unsuccessful attempts at submission**<br>***Submission time**<br>**If not apply" go to confirm payment.** | **Applicant** |
| 2 | Validation | Validate the Application accordingly.<br>Confirm that all mandatory input fields are entered. Validate all data entered for consistency.<br>Confirm applicant is registered and has valid GMP certificate.<br>Confirm applicant has current valid license.<br>Generate an Application reference number | System |

| | | | |
|---|---|---|---|
| | | and record application in the register<br>Acknowledge application | |
| 3 | Invoice for evaluation | If chargeable service:<br>Generate invoice<br>Generate Request for Payment<br>If payment exempt service:<br>Update payment status to paid. | System |
| 4 | Confirm Payment | If invoiced, Confirm payment.<br>If not yet paid go to End process<br>If paid and selection is "Print" or "Acknowledge" go to housekeeping. | System |
| **5** | **Form team** | **Constitute evaluation team**<br>**Notify team members**<br>**Request for conflict of interest declaration** | **Registrar** |
| **6** | **confirmation** | **Confirm no conflict of interest** | **Team** |
| **7** | **Review** | **Determine if Lab analysis is required and move to 8 else move 10.** | **Team** |
| **8** | **Sample submission** | **Submit Laboratory Requisition Form, Submit to the Lab and Confirm the Lab reference no.**<br>**Confirm Receipt of certificate and Invoice** | **Team** |
| 9 | Lab result | Notify client and request for payment | System |
| 10 | Invoice for lab test | If chargeable service:<br>Generate invoice<br>Generate Request for Payment<br>If payment exempt service:<br>Update payment status to paid. | System |
| 11 | Confirm Payment | If invoiced, Confirm payment.<br>If not yet paid go to End process<br>If paid and selection is "Print" or "Acknowledge" go to housekeeping. | System |
| **12** | **Evaluation** | **Review the Dossier, and approve/reject**<br>Prepare report for Board Committee<br>Forward report to board committee | **Board** |
| **12 B** | **Review Clinical Trials** | **Review clinical trials data. Drill down to data sets for confirmations** | **Board** |
| **13** | **Approval** | **Review report and approve/reject** | **Board PC** |
| 14 | License | If approved, Generate certificate<br>Notify applicant | System |
| **15** | **Confirm Gazettiment** | **Gazette the Product** | **Registrar** |
| **16** | **Confirm** | **Confirm receipt of license** | **Applicant** |
| 17 | Housekeeping | If Action is "Print" print the filled form.<br>If Action is "Acknowledge" record end time. | System |

| | | | |
|---|---|---|---|
| 18 | End process | If Action is “Apply” Note completion time. Exit the process. | System |

**Table 31: Re-engineered Drug Registration Process**

Please note STEP 12B added to make clinical trials mandatory especially drill down that does not exist in the current eCTD.

Therapeutic products are evaluated based on submitted dossiers and drug samples. The process is fairly simple. It involves receiving the product dossier, allocate a number, approve for payments, schedule the dossier for evaluation, evaluate the dossier and examine laboratory results if necessary, approve product and issue certificate. This is a flawless process until you start to examine it in details. The questions that emerge are:

1. What data do you use to determine that a product can be invoiced?
2. What happens to rejections? At what point of the process do they come back?
3. If scheduling is first in first out, what happens to fast tracking?
4. Where do clinical trials come in?

It was also not clear what the roles of each player were. It was generally assumed the Pharmacist will do evaluation and issue permit, the accountant will handle finances, the data clerks will handle clerical work and so on and so forth.

However as shown in Figure 17: New Re-Engineered Product Registration Process with Clinical Trials Input, the roles of each player were properly defined and shortened to specific processes. There is also addition of step no 12B in table Table 31: Re-engineered Drug Registration Process to ensure data from clinical trials is used and more so the drill down into the data sets that does not exist in conventional eCTD. This ensures no overlaps and proper data flow is guaranteed. Accountability and traceability was increased, as it is very easy to tell at what point the process has stalled or failed to deliver intended results.

In the re-engineered processes, clinical trials have been made a mandatory component of evaluation. Though the law does not require this, the fact that modules 4 and 5 of eCTD and CTD -that have been adopted by Kenya – demand clinical trials, which therefore means the clinical trials are implicitly mandatory.

### *5.2.3 Step3: Review and Implementation of CTR architecture to incorporate SDTM standard*

Once the policy and re-engineering has been done, the next logical item is to review and implement a new version of CTR architecture that incorporates SDTM standard. This would now allow the Board to fully store all data associated with any clinical trial done anywhere in the world and use that data for whatever decision making purposes required. Currently the data stored by the Board is not adequate for decision-making purposes.

To solve the problem of clinical trials the full version of SDTM should be implemented. Sections of CTR that are PPB specific can be maintained as mandatory data fields and applicants can only choose from other SDTM domains. To accommodate international applicants the CTR aspects can be left as optional for clinical trials conducted outside Kenya as long as the national details of the country of first clinical trials are fully filled. Alternatively the foreign based clinical trials administrative data can be added as a domain.

New process steps for clinical trials would require to mandate the board to demand for SDTM data standards as show in table Table 32: Re-Engineered Clinical Trials Processes with SDTM data requirement

| | Steps | Description | Actor |
|---|---|---|---|
| **1** | **Submit documents** | **If applying or extending submit Application for registration of clinical trials Form PPB221:**<br>**Note *Unsuccessful attempts at submission**<br>***Submission time**<br>**If not applying or extending go to confirm payment.** | **Applicant** |
| **1B** | **Submit Proposed Domains** | **Applicant shall submit proposed domain for data capture** | **Applicant** |
| 2 | Check requirements | • Confirm that all mandatory input fields are entered. Validate all data entered for consistency.<br>• Confirm that the clinical trial has been approved by the Protocol committee<br>• Generate an application number<br>• Enter the application in the register | System |
| 3 | Invoice | If chargeable service:<br>• Generate invoice<br>• Generate Request for Payment<br>If payment exempt service:<br>Update payment status to paid. | System |

| | | | |
|---|---|---|---|
| 4 | Confirm Payment | If invoiced, Confirm payment.<br>If not yet paid go to End process<br>If paid and selection is "Print" or "Acknowledge" go to housekeeping. | System |
| **5** | **Assessment** | **Review the application and approve/reject** | **Board** |
| **5B** | **Domain Concurrence** | **Concur or amend data domains** | **Board** |
| 6 | Notification | Notify the applicant of Approval/rejection | System |
| **7** | **Reporting** | **Report on Clinical Trial Progress** | **Applicant** |
| **8** | **Monitoring** | **Monitor Clinical Trial Progress** | **Board** |
| **9** | **Termination** | **Stop Clinical Trial** | **Board** |
| 11 | Housekeeping | If Action is "Print" print the filled form.<br>If Action is "Acknowledge" record end time. | System |
| 12 | End process | If Action is "Apply" Note completion time.<br>Exit the process. | System |

**Table 32: Re-Engineered Clinical Trials Processes with SDTM data requirement**

Please note step 1B that requires the applicant to submit their proposed domains and step 5B which requires the board to concur with the proposed domains or amend the proposed domains. This will ensure that the clinical trials data uses the SDTM data requirements.

The CTR and SDTM architectures that need to be implemented have been explained in detail in CHAPTER FOUR – eCTD AND CTR DATA ARCHITECTURES.

### *5.2.4 Step 4: Capacity building*

A lot of training would be required to the regulatory officers to adopt the SDTM standards in the clinical trials regulation and in the use of data mining tools to validate reports.

### *5.2.5 Step 5: Integration of CDISC SDTM to eCTD*

Integration of the CDISC SDTM to eCTD using:

a. formular to integrate the various items of SDTM to eCTD that is:

$$x = \sum_{m \in S} d(m)$$

b. Submit CDISC SDTM data to eCTD modules 4 and 5 using predetermined hierachy.

More details explained in **5.3 eCTD and CTR Architectures Integration**

## 5.3 eCTD and CTR Architectures Integration

eCTD and CTR (CTR with SDTM implemented) would be very different in terms of data stored by the repositories (database schema) implementing the architectures. The requirements of each architecture are also fundamentally different in the sense that CTR monitors the variables of a clinical trial and eCTD gets the reports of a clinical trial. Currently the practice worldwide is for the Principal Investigator to use SDTM to manage data and prepare reports for product registration. SDTM data is sent directly to regulator for clinical trial monitoring and once the clinical trials are over and successful, the data is used by the principal investigator to prepare reports for product registration as illustrated in Figure 18: World best practice in therapeutic product registration..

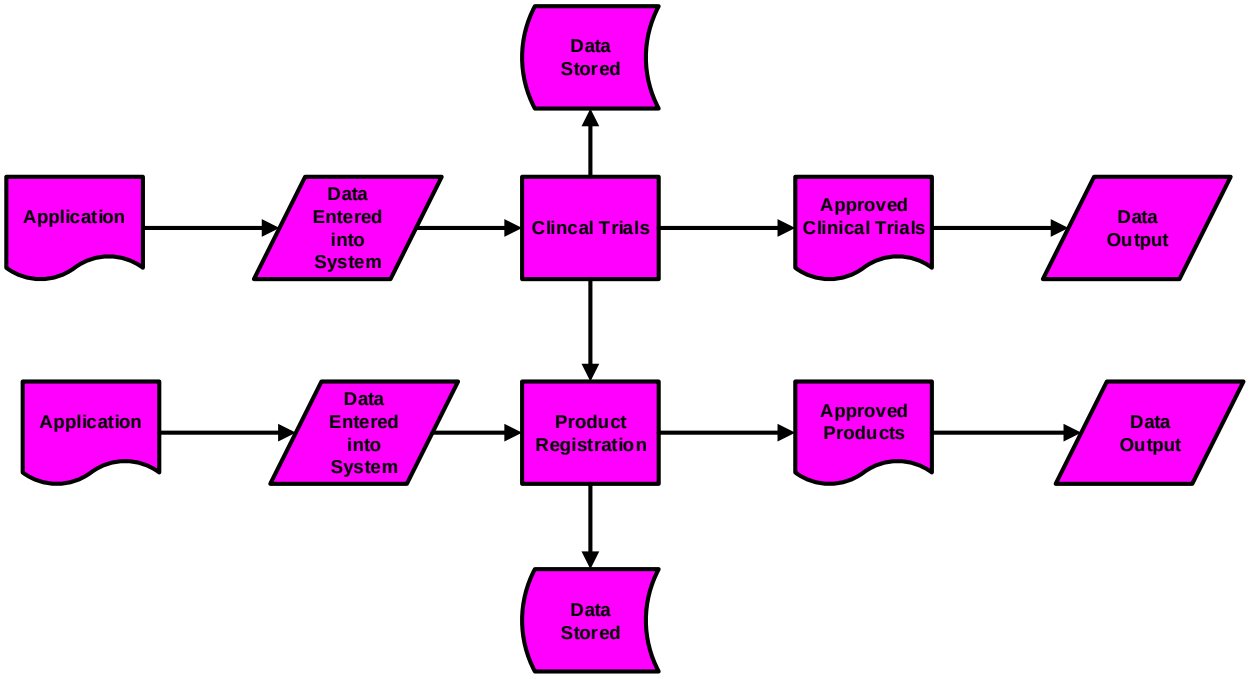


**Figure 18: World best practice in therapeutic product registration.(Ratanawijitrasin & Wondemagegnehu, 2002)**

A regulator like Pharmacy and Poisons Board will then validate reports presented during product registration against finding done in clinical trials to ascertain that the reports are a reflection of the actual clinical trial done. In order for the regulator to validate the reports, the regulator would also be required to generate reports from the clinical trials data and match the reports presented to the reports generated as illustrated in Figure 19: World best practice in repository storage and data validation.

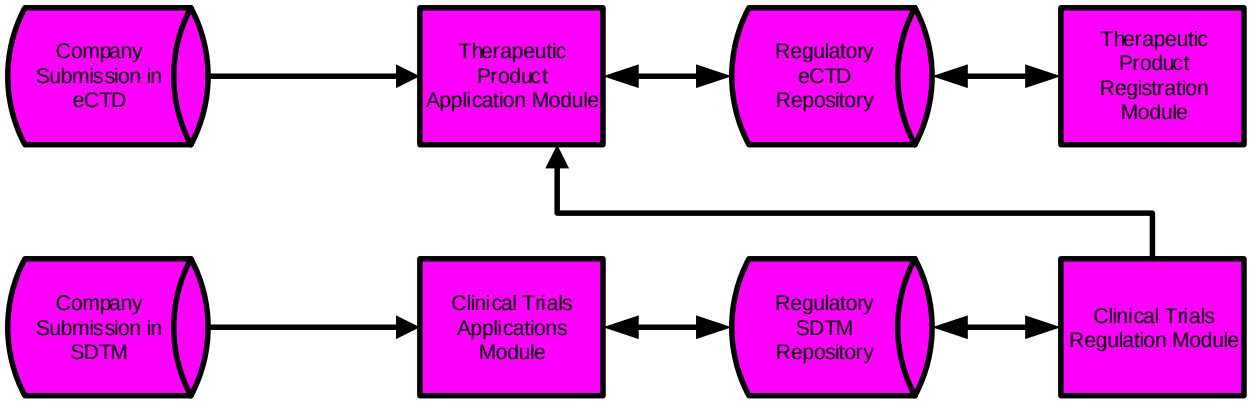


**Figure 19: World best practice in repository storage and data validation. (Ratanawijitrasin & Wondemagegnehu, 2002)**

Due to the legal setting in Kenya and partially due to lack of adequate resources, the therapeutic product registration process is slightly different to accommodate clinical trials that are not required to be regulated by law yet at the same time enforce the regulation. To do this the model will look like illustrated in Figure 20: Current Pharmacy and Poisons Board therapeutic products registration flow.

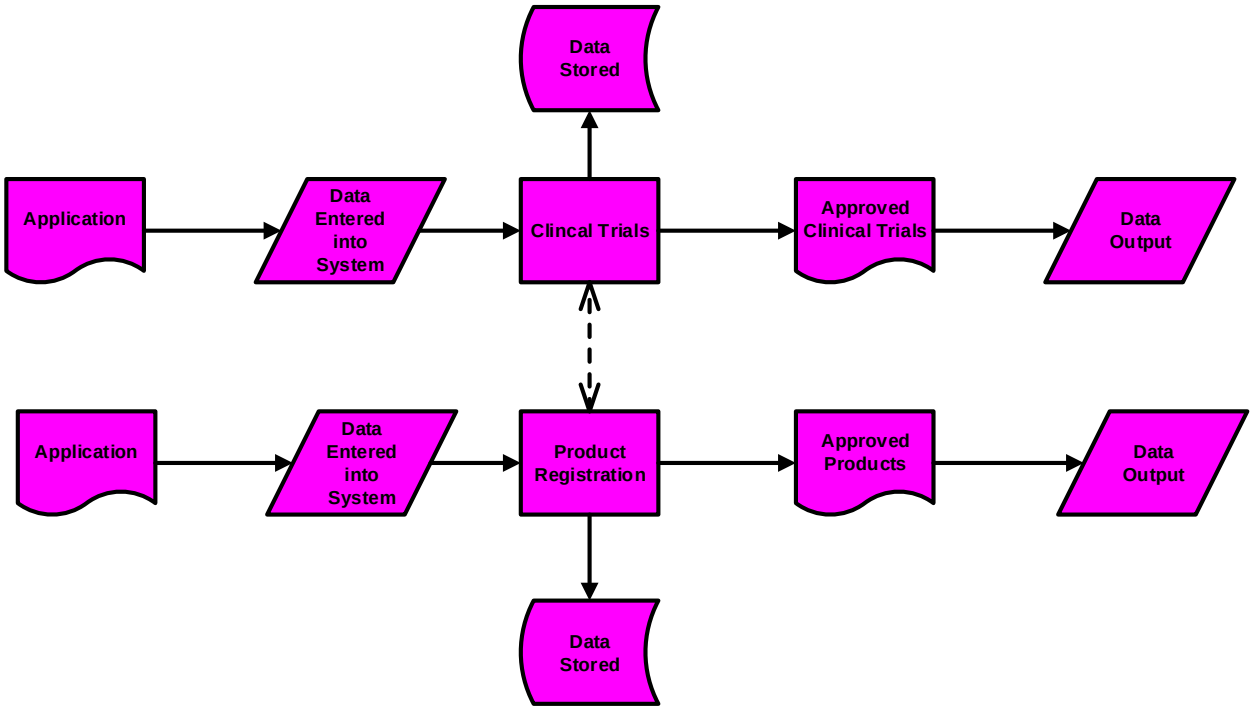


**Figure 20: Current Pharmacy and Poisons Board therapeutic products registration flow.**

Therefore the proposed solution will need a model that can accommodate the current legal requirements hence a model as illustrated in Figure 21: Proposed Common repository with eCTD and SDTM architectures implemented and legal requirements met.

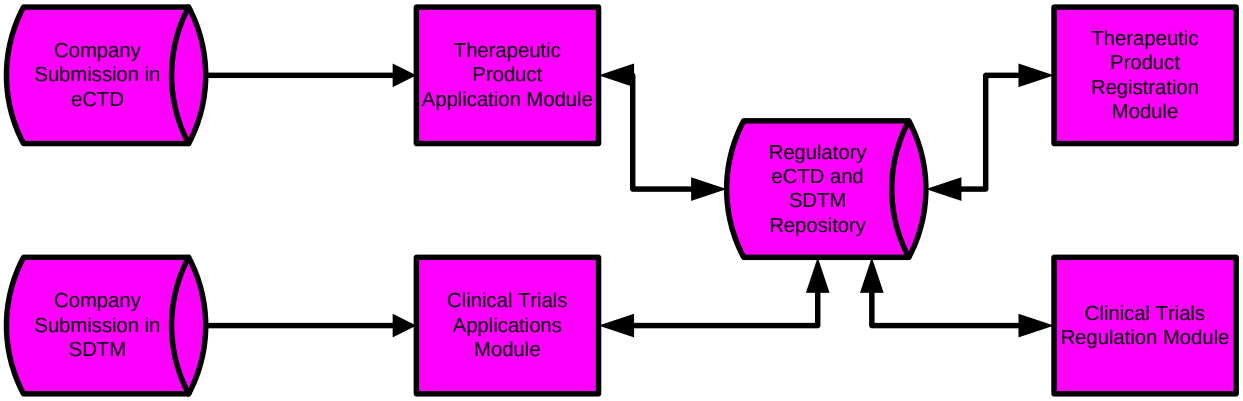


**Figure 21: Proposed Common repository with eCTD and SDTM architectures implemented and legal requirements met.**

### *5.3.1 Integration Formula*

To do this the CDISC SDTM data can be integrated into eCTD using the formula

$$x = \sum_{m \in S} d(m)$$

Where:

x = study report as expected in eCTD Module 4 and 5

S = SDTM Domain - Table 14: SDTM Domains

d = Data tabulation Data – Defined using the CDISC SDTM XML Data Definition for the data that the Principal Investigator is submitting.

m = Data Sets – SDTM data as described in 4.4.1.2 Organisation of Data

m is equal to all actual fields of SDTM data set divided by the expected fields of the SDTM data set, d is each data tabulation data item for which SDTM data sets exist and S are the SDTM domains for which the Principal investigator has selected to present data.

The total value therefore is equal to the sum total of all the data elements expected from the items the Principal Investigator has selected to present and the value of x will be equal to the total value if all elements are actually presented or less if some data elements are missing. A percentage can be calculated as:

$$\frac{\text{x}}{\text{total data elements expected}} * 100$$

The Pharmacy and Poisons Board can then fixa minimum percentage that is acceptable.

Actual flow of data would play out as illustrated in Figure 22: Integration Model based on the Godoym model with modifications to include the PPB identifiers and actual integration to module 4 or module 5. As per the illustration, the domain in SDTM are aggregated and summarised using the formula to get the final PPB summaries that are then queried or pushed to Module 4 and Module 5 of eCTD.

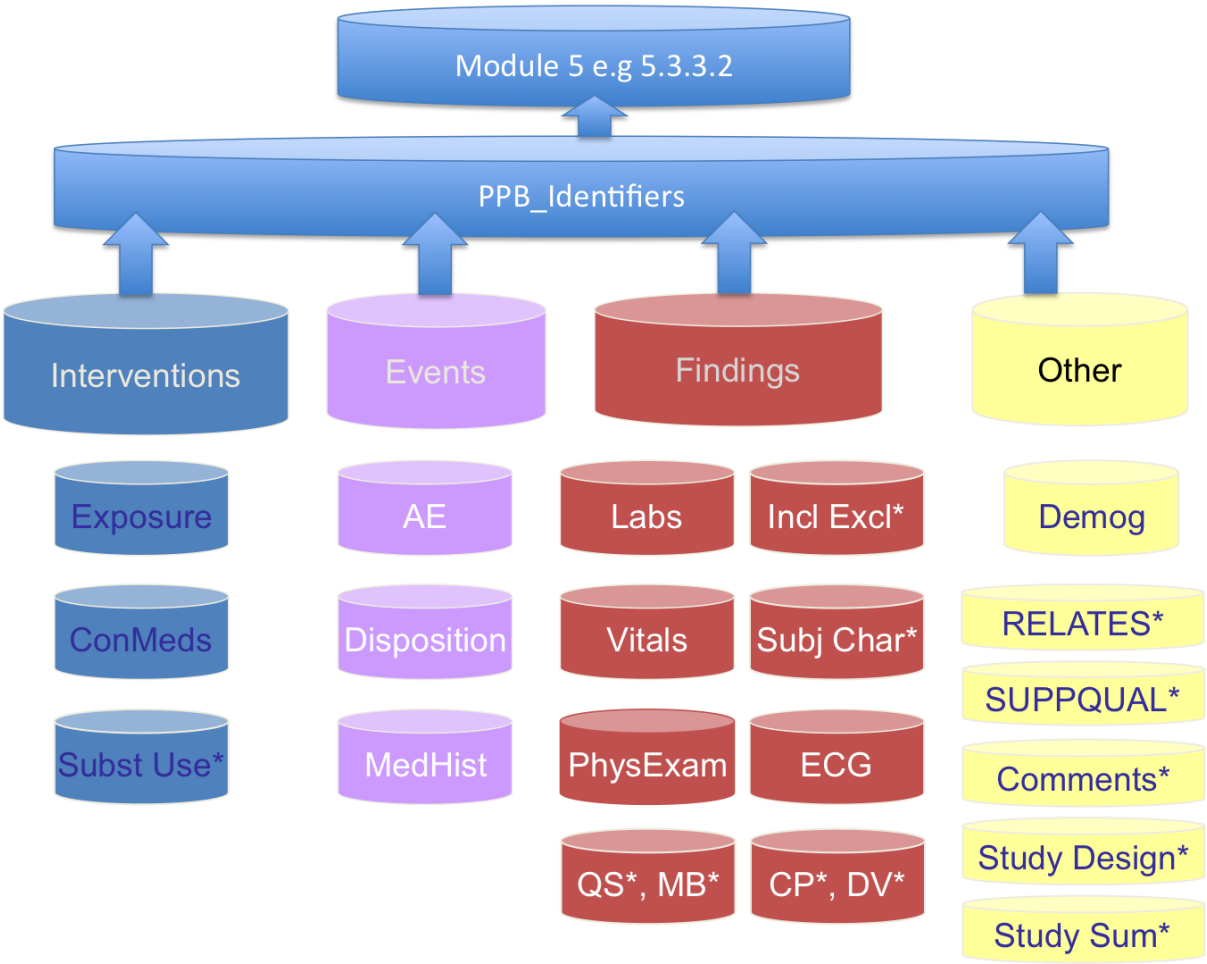


**Figure 22: Integration Model based on the Godoym model (Godoym, 2004)**

NOTE: in the above illustration - Figure 22: Integration Model based on the Godoym model domain are summarised as per PPB identifiers and this is the data that is finally available for module 4 and module 5 of the eCTD. In this way the bridge between eCTD and SDTM is created.

Sample for 5.3.2.2 Definition in eCTD

| | | |
|---|---|---|
| 296 | Number | 5. 1.3.2.2 |
| | Title | Reportsof Hepatic MetabolismandDrug Interaction Studies |
| | Element | m5-3-2-2-reports-of-hepatic-metabolism-and-drug-interaction-studies |
| | Directory | m5/53-clin-stud-rep/532-rep-stud-pk-human-biomat/5322-rep-hep-metab-interact-stud |
| | Comment | |
| 297 | Number | |
| | Title | *Study Report 1* |
| | Element | m5-3-2-2-reports-of-hepatic-metabolism-and-drug-interaction-studies |

| | | |
|---|---|---|
| | Directory | m5/53-clin-stud-rep/532-rep-stud-pk-human-biomat/5322-rep-hep-metab-interact-stud/*study-report-1* |
| | Comment | |
| 298 | Number | |
| | Title | *Study Report 2* |
| | Element | m5-3-2-2-reports-of-hepatic-metabolism-and-drug-interaction-studies |
| | Directory | m5/53-clin-stud-rep/532-rep-stud-pk-human-biomat/5322-rep-hep-metab-interact-stud/*study-report-2* |
| | Comment | |
| 299 | Number | |
| | Title | *Study Report 3* |
| | Element | m5-3-2-2-reports-of-hepatic-metabolism-and-drug-interaction-studies |
| | Directory | m5/53-clin-stud-rep/532-rep-stud-pk-human-biomat/5322-rep-hep-metab-interact-stud/*study-report-3* |
| | Comment | |

**Table 33: Sample for 5.3.2.2 Definition in eCTD**

**Document Definition For 5.3.2.2**

```
<!ELEMENT m5-3-2-reports-of-studies-pertinent-to-
pharmacokinetics-using-human-biomaterials (leaf*, m5-3-
2-1-
plasma-protein-binding-study-reports?, m5-3-2-2-reports-
of-hepatic-metabolism-and-drug-interaction-studies?, m5-
3-
2-3-reports-of-studies-using-other-human-biomaterials?)>
<!ATTLIST m5-3-2-reports-of-studies-pertinent-to-
pharmacokinetics-using-human-biomaterials
%att;
>
<!ELEMENT m5-3-2-1-plasma-protein-binding-study-
reports ((leaf | node-extension)*)>
<!ATTLIST m5-3-2-1-plasma-protein-binding-study-
reports
%att;
>
<!ELEMENT m5-3-2-2-reports-of-hepatic-metabolism-
and-drug-interaction-studies ((leaf | node-extension)*)>
<!ATTLIST m5-3-2-2-reports-of-hepatic-metabolism-and-
drug-interaction-studies
%att;
>
```

**Sample Definition for the Haemophilia B**

```
<?xml version="1.0" encoding="ISO-8859-1"?>

<?xml-stylesheet type="text/xsl" href="define1-0-0.xsl"?>

<ODM


<ItemGroupDef OID="HAEMOPHILIA B"

 Name="123LAB2TESTS"

 Repeating="No"

 IsReferenceData="No"

 Purpose="Tabulation"

 def:Label="Haemophilia B"

 def:Structure="One record per subject"

 def:DomainKeys="STUDYID USUBJID"

 def:Class="Special Purpose"

 ...
```

The sample definition above would fit into a domain data tables as shown in Table 34: Haemophilia B Sample Table

| Data Set | Description | Structure | Purpose | Keys | Class |
|---|---|---|---|---|---|
| HAEMOPHILIA B | 123LAB2TESTS | One record per subject | Tabulation | STUDYID USUBJID | Special Purpose |

**Table 34: Haemophilia B Sample Table**

From the above domain table, data about each subject would be gathered in a format similar to this format displayed by SAS sample

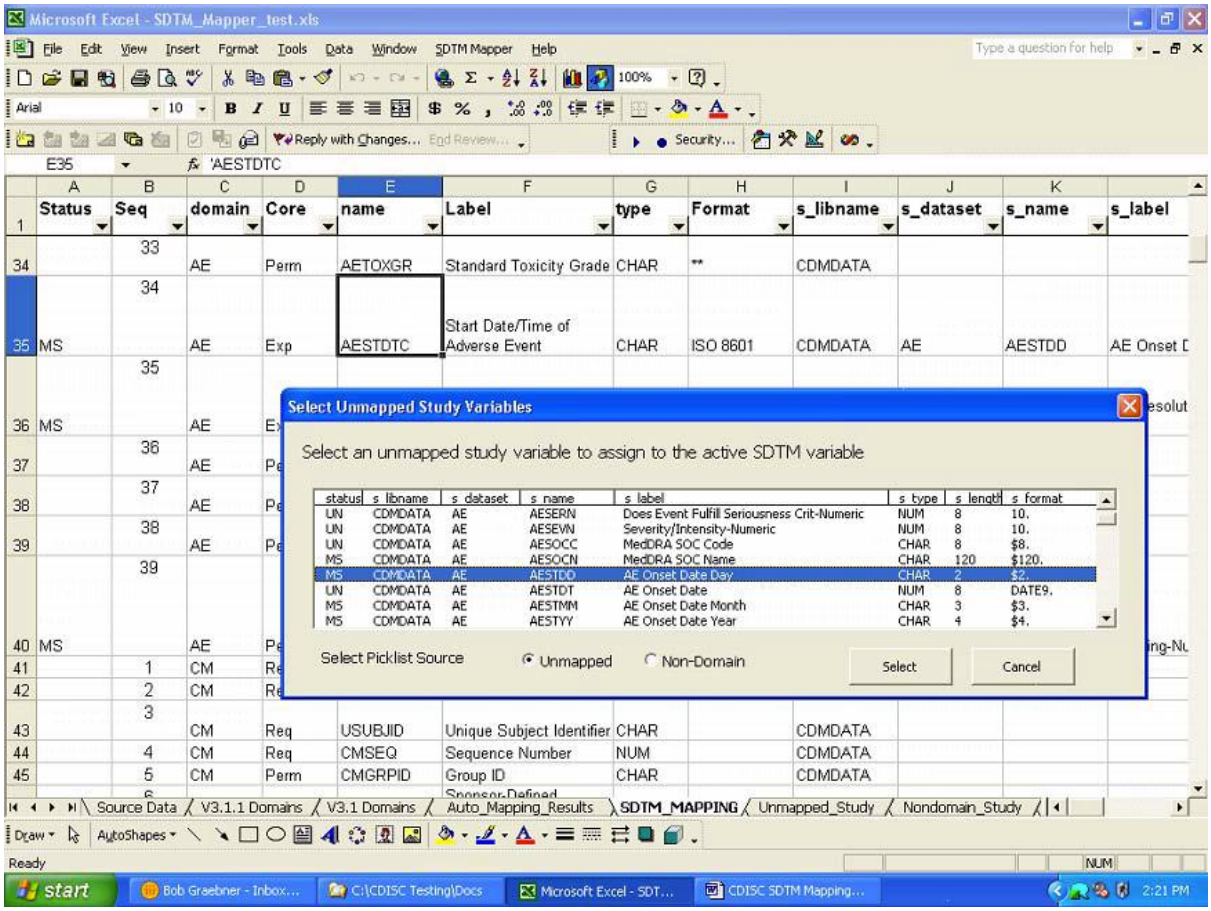


**Figure 23: SAS Sample data(Graebner, 2008)**

### *5.3.2 Submission Hierarchy*

The hierarchy that would be produced when the above formula is used is:

- Clinical Study Reports (x)
  - SDTM (s)
    - Data Tabulation Data (d)
      - **Data Tabulation Datasets (ds)**

To achieve the submissions from CDISC to eCTD as simple tool as Microsoft Excel can be used to prepare the submissions as longs the XML data definition follows the SDTM standard.

### *5.3.3 Common Repository*

Unlike the FDA that uses two different repositories, my proposed approach is to have one repository with the two architectures in it as show in Figure 24: Shared Repository.

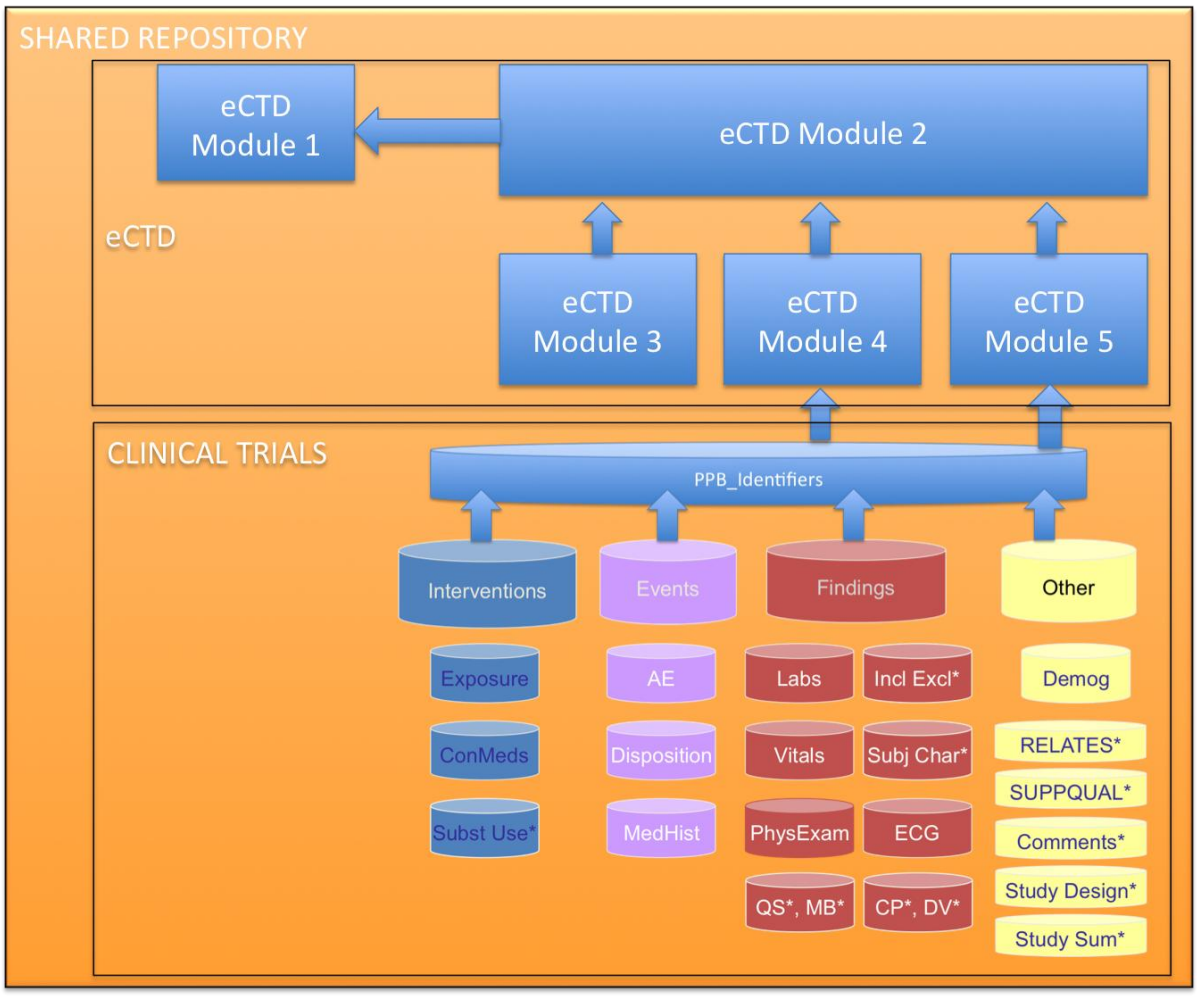


**Figure 24: Shared Repository**

Having two architectures sharing one Repository will help meet the legal requirement that makes clinical trials regulation optional and at the same time allow for the implementation of the eCTD and SDTM standards in full.

### *5.3.4How the Common Repository will Work*

How will this shared repository work?

From the example of Haemophilia B clinical studies a sample prototype of a hypothetical therapeutic product that is used to treat Haemophilia B can be created to test the data flow. The hypothetical Haemophilia B drug is called Haemostop prepared by a hypothetical company called Madawanguvu Pharma.

Madawanguvu Pharma needs to have Haemostop registered. The first step is to conduct clinical trials and gather clinical data. Assuming that the clinical trials have gone through the normal phases that they go through and all data necessary has been captured, this is how the scenario will play out.

The principal researcher – hypothetical Dr. Akili - at Madawanguvu will register clinical trials. Dr. Akili will propose the domains for which he beliefs are necessary to capture data of the clinical trials form Haemostop. He will forward the proposal to the regulator and upon discussions the regulator will approve the domains for which the data will be captured and allow Dr. Akili to proceed. These domains are SDTM domains and referred as ‘s’ in the integration formula in 5.3.1 Integration Formula and as ‘SDTM(s)’ in the submission hierarchy in 5.3.2 Submission Hierarchy.

Dr. Akili will then proceed to tabulate these domains and create data tabulations for these domains that are referred to as ‘d’ in the integration formula and as data tabulation in the submission hierarchy.

From the tabulations, Dr. Akili will start to record his data in data sets per each tabulation which is part of each domain. These data sets are referred to as ‘m’ in the integration formular and ‘m’ in the submission hierarchy.

So, how does the actual data come in?

After Dr. Akili has done all the definitions as explained above, he can now capture his data in any software that will allow him to produce XML files like Microsoft Excel. If Dr. Akili uses Microsoft Excel, he will have to define all the data fields as expected by SDTM standard that collectively will be referred to as ‘m’ or SDTM dataset.

In the haemophilia example used in this research, lab tests that are under the data set called HAEMOPHILIA B, and the lab tests could be:

| **id** | **Data_set_id** | **Staining_Round** | **Start_Colour** | **End_Colour** |
|---|---|---|---|---|
| 1 | 3 | 1 | None | White |
| 2 | 3 | 2 | None | Grey |

| {{other records in the data set may be between 3 and 1023}} | | | | |
|---|---|---|---|---|
| 1024 | 3 | 1024 | orange | Umber/red |

Different data sets will be developed and tabulated based on the tabulation data in this case for the set Haemophilia that is data set id no 3.

This data can be exported to XML from Microsoft Excel.

<?xml version="1.0" encoding="ISO-8859-1"?>

<?xml-stylesheet type="text/xsl" href="define1-0-0.xsl"?>

<ODM

<ID="1"

data_set_id="3"

stainig_round="1"

start_colour="none"

end_colour="white"

/>

<ID="2"

data_set_id="3"

stainig_round="2"

start_colour="none"

end_colour="grey"

/>

...

This XML is generated using predefined SDTM XML formats as explained in 4.4.1.2 Organisation of Data.Data will continue for each and every record.

Since Dr. Akili had defined his domains very well, his data tabulation very well and finally his data sets very well, the system will read the XML file output and by following the relationships in the records e.g. data_set_id, will be able to aggregate the data as required in the submission hierarchy in 5.3.2 Submission Hierarchy. Which is:

1. all data sets first ‘m’
2. followed by all tabulations ‘d’ of each ‘m’
3. followed by domains ‘s’ of each ‘d’

Clinical trials repository now ends once we get the domains ‘s’.

So how does it cross over to the eCTD or Therapeutic products?

According to the proposed formula, and eCTD module, that is module 4 or module 5, is a summation of the data per every domain required.

As per eCTD, the study reports will be based on the agreed modules that the regulator approved for study. In the examples used in this research show here:

**Document Definition For 5.3.2.2**

```
<!ELEMENT m5-3-2-reports-of-studies-pertinent-to-
pharmacokinetics-using-human-biomaterials (leaf*, m5-3-
2-1-
plasma-protein-binding-study-reports?, m5-3-2-2-reports-
of-hepatic-metabolism-and-drug-interaction-studies?, m5-
3-
2-3-reports-of-studies-using-other-human-biomaterials?)>
<!ATTLIST m5-3-2-reports-of-studies-pertinent-to-
pharmacokinetics-using-human-biomaterials
%att;
>
<!ELEMENT m5-3-2-1-plasma-protein-binding-study-
reports ((leaf | node-extension)*)>
<!ATTLIST m5-3-2-1-plasma-protein-binding-study-
reports
%att;
>
<!ELEMENT m5-3-2-2-reports-of-hepatic-metabolism-
and-drug-interaction-studies ((leaf | node-extension)*)>
<!ATTLIST m5-3-2-2-reports-of-hepatic-metabolism-and-
drug-interaction-studies
```

%att;
>

It is clear for Haemostop to be registered using eCTD, PLASMA PROTEIN BINDING STUDY REPORTS (element m5-3-2-1) are needed in module 5 of eCTD hence the 5-3-2-1 reference of the element which is equal to 5.3.2.1 in the eCTD modules definition. This means Dr. Akili had declared the domain LB (Laboratory Results) under the domain LB of SDTM of CTR and he will need data sets for tabulating Plasma Protein Binding.

So using the above example, Module 5 section 5.3.2.1 will be a summary report of Plasma Protein Binding, which will be generated from data sets under the domain ('s') called LB or Laboratory Results. Therefore we can say each and every single laboratory test that will be done to test Plasma Protein Binding, will be under the domain LB which in the case of our formula is 's' and tabulated under Plasma Protein Binding.

Since this is an integrated environment, the software used should be able to read or drill down into the CTR repository for all XML leaves of LB domain and get all data related to the tabulation of Plasma Protein Binding.

What does this mean?

Unlike the current system where the report presented in the eCTD dossier is final and if an evaluator needs more data he/she has to go the CTR to start perusing, the proposed system will have no fixed summaries but auto generated summaries that the evaluator can create to meet his/her immediate need. Therefore if an evaluator is not comfortable with the summary created by the researcher like Dr. Akili, the evaluator can drill down and create their own new summary for comparative purposes form the data presented while at the same time retaining control of the data at hand.

Though Microsoft Excel has been used in the Haemostop example, full implementation is done in regular relational databases, JSON and any database system with XML outputs to meet the ICH and CDISC standards.

## 5.4 Data Schema Merging and why it would not be appropriate.

### *5.4.1 Schema Merging*

Schema merging is the process of integrating several schemas into a common, unified schema. There have been various approaches to schema merging, focusing on particular modelling languages, or using a lightweight, abstract metamodel. Refer to 2.0.19Schema Merging.

### *5.4.2 Schema Merging Drawbacks in eCTD and CTR Architectures*

The reasons why schema merging of the schemas implementing eCTD and CTR would not be appropriate are:

1. These are two different standards with different requirements.
2. Data from one repository is not required in the other repository, just a report that is generated.
3. Internationally the schemas of the two architectures are never merged. Actually the two architectures are developed by two different organisations and in very large regulatory agencies like the FDA, Swissmedic of Switzerland and Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom (UK), the departments that implement eCTD and CTR function more or less like independent agencies. So merging schemas would deny the Board the benefits of international standardisations and may lead to non conformity.

## 5.5 Benefits of Integration.

There is one benefit of integration the eCTD and CTR architectures; electronic validation of clinical trial reports during product evaluation. Currently this is not being done since adequate data does not exist and the business processes do not allow for integration and subsequent validation.

# CHAPTER SIX – DISCUSSION, CONCLUSION AND RECOMMENDATION

## 6.1Discussion

This research proposed a very pragmatic way of solving a very complex problem, a solution that can actually be viewed as a stopgap measure. The actual issue here is having the therapeutic products regulation framework reviewed from an Information Technology perspective. In its current state, the regulatory framework still treats computer managed data and information in the same manner that the paper based system did. The electronic version is just an implementation of the paper-based system with just a few "major" changes: eCTD is just CTD in electronic form and SDTM is a clinical research notes exchange.

Major issues that have lend to the current state are:

1. Legal framework that does not require for clinical trials to be part of the product evaluation process.
2. Traditional approach to regulation where independence of institutions means independence of data and information, a territorial/jurisdiction approach.

To realise the proposals of this research, the implementation will have to overcome a number of critical challenges. These challenges are:

1. Interface – different standards propose different standards of their interfaces for user access and data exchange. Different countries and agencies implement these interfaces differently. Though it is fairly easy to exchange data using a standardised data format, the point of exchanges may differ so much to a point of being confusing. The current implementation of either SDTM or eCTD shows this problem where each country provides a different interface for the same data to the same industry player. So how does Kenya develop the interface for SDTM and how does it improve the interface for eCTD to meet international standards? How will the integrated interface look like?
2. Submission – this melts down to the human being responsible for the information passed on to the regulatory authority. In most countries companies are asked to nominate a focal person and mostly an individual in the regulatory section of the company. In Kenya this is usually the regulatory pharmacist. However in reality the documents are prepared by many officers under the supervision of the accredited person. In an integrated environment this means there are more persons involved in

this case the regulatory pharmacist and the principal investigator. Currently the PPB recognises both but that may not be the case once integration is done and the repository is one. There can only be one account manager per repository not two, or may be the rules can be changed to allow more than one account manager with differing responsibilities.

3. Data Volumes – Integration reduces the duplication of data however this brings yet another challenge, increased data. Reduced duplication means the need for more data to validate a process. Clinical trials are likely to generate more data since no summaries will be required and the data will be used as is.
4. Stakeholder and Regulatory Buy-in – eCTD and SDTM are fairly new standards and that are being implemented worldwide. To get buy-in for implementing these standards, they had to be developed to replicate the paper standards that existed. Therefore moving from what is currently available and that is still undergoing some level of development means a lot of engagements with all parties to make a breakthrough.
5. Financial Implications – all standards are costly to implement. The true cost of integration at the moment would be difficult to predict.

## 6.2Conclusion

"The only thing that is constant is change" – Heraclitus. With the overwhelming presence of information management systems in the modern world, therapeutic products regulation has only one option, adopt information management in its totality and in the best way that ensures efficiency and effectiveness.

Change is inevitable and what matters is how it is managed. With the right kind of technology, political support and finances, the integrated regulatory information management framework can be done.

## 6.3Recommendations

Recommendations can be placed into two categories, Recommendations for Kenya, Recommendations for the International Standards and Recommendations for implementation.

### *6.3.1 Recommendations for Kenya*

1. Clinical trials should be done continuously during the product development and not waiting to receive the data during therapeutic product evalution.
2. In the cases whereactual continuous monitoring is not possible due to international requirements, data should be submitted electronically during the trial period.
3. Legal framework should be changed to make clinical trials mandatory during product evaluation.
4. Full implementation of the CDISC SDTM standards should be done.

### *6.3.2 Recommendations for International Standards*

1. Information management for regulatory standards should be viewed from an Informatics perspective to avoid fragmentation of data systems that is not necessary and detrimental.
2. Information management for regulation needs to be separated from the standards development process. The design of information management system does not need to reflect the standards but to facilitate the implementation of the standards in the best way possible to the implementing agency. What this means is that there can be different standards, managed by different agencies with a common information management framework to the different standards.

### *6.3.3 Recommendations for Implementation*

Implementation of any standard is very important and the most critical phase of the process. To implement an integrated framework a few recommendations would be handy.

1. Change Management – Technology changes very rapidly. It therefore important to manage this change. To do that planning for change is very important as well as taking all the parties involved through the change process. Start with the non-controversial issues and easy to accept changes that make the most impact. In the case of integration, cost reduction areas would be the best areas to start. Areas of reduced workload will follow these and the areas of regulatory jurisdictions would come at the end.

   In the pharmaceutical regulation area, politics always take centre stage. These are both local and international and can derail even the most well-intentioned programmes. Managing political change needs an understanding of the regulatory

playing field and strategizing to manage political fears before the project starts and political manoeuvres during and near the end of the project.

2. Avail the technology– it is always best to avail the technology upfront. Since medicines regulation has been in place for sometime now and technologies exist including regulatory bodies having their own in-house technologies,modifications of what is already existing would be very easy and have a platform ready as major changes take place gradually.
3. Start with new applications – always start with the new application for registration. If possible let also the new companies move to the new platform first. Migrating of the older applications and companies can also be done gradually.

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## APPENDIX 1 – EAC E-Readiness Assessment Tool

### General Infrastructure and Operational Tools Assessment Questionnaire

| | | Countries (NMRAs) | | | | | |
|---|---|---|---|---|---|---|---|
| **No** | **Section to cover** | **Burundi** | **Kenya** | **Rwanda** | **Uganda** | **Tanzania Mainland** | **Zanzibar** |
| **1** | **OrganizationalICT policy andstrategy** | | | | | | |
| | Is ICT explicitly mentioned in the vision, mission, mandate, core valuesor strategic objectives ofyourorganization? | | | | | | |
| | Doesyour institution have anICT policy? | | | | | | |
| | Ifyes in (b), doyou haveanICT policyimplementation plan? | | | | | | |
| | Doesyour institution have anICT strategy? | | | | | | |
| **2a** | **NMRAs Infrastructure Capacity** | | | | | | |
| | Hardware &software Hosting Services (Do you Host in national Data Center or in your Premises) | | | | | | |
| | Networkdesign &security (the Capacity of NMRAs Internal Network and Internet Capacity) | | | | | | |
| | Website design &security | | | | | | |
| | Internetsecurity (how the web based Applications are Secured) | | | | | | |
| | Securityand antivirus | | | | | | |
| | Staffdigitalaccess targets | | | | | | |
| | Emailand communicationpolicy | | | | | | |
| | ICTShared services | | | | | | |
| | Disaster recovery facilitation for NMRAs | | | | | | |
| **2b** | **Existing ICT infrastructure/ Resources** | | | | | | |
| | Desktop Computers (Number of Working PCs) | | | | | | |
| | Servers and Storage Capacty (existing Servers and Capacity) | | | | | | |
| | Printers (No of Working Printers) | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Office automation | | | | | | |
| | Local Area Network (functioning LAN) | | | | | | |
| | Wide Area Network(Capacity of NMRA office to Connect to out site office) | | | | | | |
| | End UserDevices(includinglaptops, I pads, smartphones) | | | | | | |
| | CommunicationDevices: VC equipment, PABX,landline, telephonesetc. | | | | | | |
| | Office Internet Connection Type (Fiber optic, modems, Wimax etc) | | | | | | |
| | Cloud Technology and Virtualization | | | | | | |
| | Internet Bandwidth | | | | | | |
| | Technology support for Hosing services | | | | | | |
| **3** | **UseofComputers** | | | | | | |
| | Howmany ofyourstaffrequiresacomputerinordertocarry outNMRAsdaily work? | | | | | | |
| | Howmany ofthesestaffhasbeenissuedwithapersonalcomputerforofficial work? | | | | | | |
| | Forstaffthatdonotneedacomputertoexecutetheirwork,howdothey access a computer to check their email and other administrative needs? | | | | | | |
| **4** | **Broadbandpenetration** | | | | | | |
| | What is your institution's broadband download/uploadinternetconnect ivity speed? | | | | | | |
| | What is your institution's number of users connected to internet? | | | | | | |
| **5** | **IT security**<br>**(**Which of the following security types are configured for the institut ion's) | | | | | | |
| | Software firewall/ Hardwarefirewall | | | | | | |
| | Intrusiondetectionsystem | | | | | | |
| | DemilitarizedZone | | | | | | |
| | Enterprise virusprotection | | | | | | |
| | Single-uservirusprotectiononallPCs | | | | | | |
| | LDAP to provide a central point of access for services for user | | | | | | |
| | Others(pleasedescribe) | | | | | | |
| **6** | **Servicehosting**<br>Whereis the Institution Host its Applications? | | | | | | |
| | Internally | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Governmentdata center | | | | | | |
| | Private host(statewhich) | | | | | | |
| | Other (specify)…… | | | | | | |
| | WhatsecurityplatformisbeingusedbythehosttoprotecttheApplications: | | | | | | |
| **7** | **Organizational ICTliteracy** | | | | | | |
| | Hasyour Institutionadopted ameasureofICT literacy?(Yes / No) | | | | | | |
| | IfYes, Pleasedescribethis measure | | | | | | |
| | PleaseestimatethepercentageofyourstaffwhomyouwoulddescribeasICT Literate | | | | | | |
| **8** | **Accessto ICT tools outsidework** | | | | | | |
| | DoesyourinstitutionfacilitateitsstafftohaveaccesstoICTswhenoutside work place? Yes / No. | | | | | | |
| | Ifyes in (above), tick allthatapplyin your institution( Laptop /PC/Ipad, Smart phones, Broadband modem) | | | | | | |
| **9** | **Data protection and privacy** | | | | | | |
| | Hasyourinstitutionwrittendownproceduresandguidelinesforthemaintenance of confidentiality,integrityandavailabilityofIT-storedbusinessinformation? Yes /No | | | | | | |
| | Doesyour institution havea policyfordata protection and privacy?Yes /No | | | | | | |
| | Havethesepoliciesandguidelinesbeendisseminatedtoallstaffmembers ?Yes/ No. | | | | | | |
| | DoyourstaffsignanydocumentscommittingthemselvestoadheretoyourICT policies and guidelines?Yes / No | | | | | | |
| | | | | | | | |
| **10** | **ICT Capacity area building (**HowmanyICTofficershave beentrainedunder the followingprofessionalcategories?) | | | | | | |
| | IT systemssecurity (Industry Certifications) | | | | | | |
| | Systemsadministration and Databaseadministration (Industry Certifications) | | | | | | |
| | Other please specify | | | | | | |

## APPENDIX 2 – Capability Maturity Model

**Capability Maturity Model**

| **Respondent Background** |
|---|
| |
| Position in organisation of the respondent(s). 1. PROJECT OR TEAM LEADER MANAGER, 2. TECHNICAL MEMBER SOFTWARE ENGINEERING PROCESS, 3. GROUP (SEPG) MEMBER and 4. OTHER) |
| Areas respondent(s) are currently working in. (1. SOFTWARE REQUIREMENTS, 2. SOFTWARE QUALITY ASSURANCE, 3. SOFTWARE DESIGN, 4. CONFIGURATION MANAGEMENT, 5. CODE AND UNIT TEST, 6. SOFTWARE PROCESS IMPROVEMENT, 7. TEST AND INTEGRATION, 8. OTHER) |
| Have respondent(s) received any CMM training |
| Software past experience |
| Previous software assessment experience. |
| |
| Noted systems the respondent(s) has had a chance to interact. |
| |
| **Does the respondent(s) have experience in the following areas:** |
| Requirements Management |
| Software Project Planning |
| Software Project Tracking and Oversight |
| Software Subcontract Management |
| Software Quality Assurance |
| Software Configuration Management |
| Organization Process Focus |
| Organization Process Definition |
| Training Program |
| Integrated Software Management |
| Software Product Engineering |
| Intergroup Coordination |
| Peer Reviews |
| Quantitative Process Management |
| Software Quality Management |
| Defect Prevention |
| Technology Change Management |
| Process Change Management |

## APPENDIX 3 – SDTM Data Schema

| Interventions Observations Classes | | | --TOXGR | Toxicity Grade | Char |
|---|---|---|---|---|---|
| **Variable Name** | **Variable Label** | **Type** | --SEV | Severity | Char |
| **Topic Variable** | | | --DTHREL | Relationship to Death | Char |
| --TRT | Name of Treatment | Char | --LLOQ | Lower Limit of Quantitation | Num |
| **Qualifier Variables** | | | --ULOQ | Upper Limit of Quantitation | Num |
| --MODIFY | Modified Treatment Name | Char | --EXCLFL | Exclude from Statistics | Char |
| --DECOD | Standardized Treatment Name | Char | --REASEX | Reason for Exclusion from Statistics | Char |
| --MOOD | Mood | Char | "Findings About" Events or Interventions | | |
| --CAT | Category | Char | **Variable Name** | **Variable Label** | **Type** |
| --SCAT | Subcategory | Char | --OBJ | Object of the Observation | Char |
| --PRESP | Pre-specified | Char | Identifiers for All Classes | | |
| --OCCUR | Occurrence | Char | **Variable Name** | **Variable Label** | **Type** |
| --STAT | Completion Status | Char | STUDYID | Study Identifier | Char |
| --REASND | Reason Not Done | Char | DOMAIN | Domain Abbreviation | Char |
| --INDC | Indication | Char | USUBJID | Unique Subject Identifier | Char |
| --CLAS | Class | Char | POOLID | Pool Identifier | Char |
| --CLASCD | Class Code | Char | SPDEVID | Sponsor Device Identifier | Char |
| --DOSE | Dose | Num | --SEQ | Sequence Number | Num |
| --DOSTXT | Dose Description | Char | --GRPID | Group ID | Char |
| --DOSU | Dose Units | Char | --REFID | Reference ID | Char |
| --DOSFRM | Dose Form | Char | --SPID | Sponsor-Defined Identifier | Char |
| --DOSFRQ | Dosing Frequency per Interval | Char | --LNKID | Link ID | Char |
| --DOSTOT | Total Daily Dose | Num | --LNKGRP | Link Group ID | Char |

| | | | | | |
|---|---|---|---|---|---|
| --DOSRGM | Intended Dose Regimen | Char | Timing Variables for All Classes | | |
| --ROUTE | Route of Administration | Char | **Variable Name** | **Variable Label** | **Type** |
| --LOT | Lot Number | Char | VISITNUM | Visit Number | Num |
| --LOC | Location of Dose Administration | Char | VISIT | Visit Name | Char |
| --LAT | Laterality | Char | VISITDY | Planned Study Day of Visit | Num |
| --DIR | Directionality | Char | TAETORD | Planned Order of Element within Arm | Num |
| --PORTOT | Portion or Totality | Char | EPOCH | Epoch | Char |
| --FAST | Fasting Status | Char | --DTC | Date/Time of Collection | Char |
| --PSTRG | Pharmaceutical Strength | Num | --STDTC | Start Date/Time of Observation | Char |
| --PSTRGU | Pharmaceutical Strength Units | Char | --ENDTC | End Date/Time of Observation | Char |
| --TRTV | Treatment Vehicle | Char | --DY | Study Day of Visit/Collection/Exam | Num |
| --VAMT | Treatment Vehicle Amount | Num | --STDY | Study Day of Start of Observation | Num |
| --VAMTU | Treatment Vehicle Amount Units | Char | --ENDY | Study Day of End of Observation | Num |
| --ADJ | Reason for Dose Adjustment | Char | --DUR | Duration | Char |
| The Events Observation Class | | | --TPT | Planned Time Point Name | Char |
| **Variable Name** | **Variable Label** | **Type** | --TPTNUM | Planned Time Point Number | Num |
| **Topic Variable** | | | --ELTM | Planned Elapsed Time from Time Point Ref | Char |
| --TERM | Reported Term | Char | --TPTREF | Time Point Reference | Char |
| **Qualifier Variables** | | | --RFTDTC | Date/Time of Reference Time Point | Char |
| --MODIFY | Modified Reported Term | Char | --STRF | Start Relative to Reference Period | Char |
| --LLT | Lowest Level Term | Char | --ENRF | End Relative to Reference Period | Char |
| --LLTCD | Lowest Level Term Code | Num | --EVLINT | Evaluation Interval | Char |
| --DECOD | Dictionary-Derived Term | Char | --EVINTX | Evaluation Interval Text | Char |
| --PTCD | Preferred Term Code | Num | --STRTPT | Start Relative to Reference Time Point | Char |
| --HLT | High Level Term | Char | --STTPT | Start Reference Time Point | Char |
| --HLTCD | High Level Term Code | Num | --ENRTPT | End Relative to Reference Time Point | Char |
| --HLGT | High Level Group Term | Char | --ENTPT | End Reference Time Point | Char |

| | | | | | |
|---|---|---|---|---|---|
| --HLGTCD | High Level Group Term Code | Num | --STINT | Planned Start of Assessment Interval | Char |
| --CAT | Category | Char | --ENINT | Planned End of Assessment Interval | Char |
| --SCAT | Subcategory | Char | --DETECT | Time in Days to Detection | Num |
| --PRESP | Pre-specified | Char | The Demographics Domain | | |
| --OCCUR | Occurrence | Char | **Variable Name** | **Variable Label** | **Type** |
| --STAT | Completion Status | Char | **Identifier Variables** | | |
| --REASND | Reason Not Done | Char | STUDYID | Study Identifier | Char |
| --BODSYS | Body System or Organ Class | Char | DOMAIN | Domain Abbreviation | Char |
| --BDSYCD | Body System or Organ Class Code | Num | USUBJID | Unique Subject Identifier | Char |
| --SOC | Primary System Organ Class | Char | **Topic Variables** | | |
| --SOCCD | Primary System Organ Class Code | Num | SUBJID | Subject Identifier for the Study | Char |
| --LOC | Location of Event | Char | **Qualifier Variables** | | |
| --LAT | Laterality | Char | RFSTDTC | Subject Reference Start Date/Time | Char |
| --DIR | Directionality | Char | RFENDTC | Subject Reference End Date/Time | Char |
| --PORTOT | Portion or Totality | Char | RFXSTDTC | Date/Time of First Study Treatment | Char |
| --PARTY | Accountable Party | Char | RFXENDTC | Date/Time of Last Study Treatment | Char |
| --PRTYID | Identification of Accountable Party | Char | RFICDTC | Date/Time of Informed Consent | Char |
| --SEV | Severity/Intensity | Char | RFPENDTC | Date/Time of End of Participation | Char |
| --SER | Serious Event | Char | DTHDTC | Date/Time of Death | Char |
| --ACN | Action Taken with Study Treatment | Char | DTHFL | Subject Death Flag | Char |
| --ACNOTH | Other Action Taken | Char | SITEID | Study Site Identifier | Char |
| --ACNDEV | Action Taken with Device | Char | INVID | Investigator Identifier | Char |
| --REL | Causality | Char | INVNAM | Investigator Name | Char |
| --RELNST | Relationship to Non-Study Treatment | Char | BRTHDTC | Date/Time of Birth | Char |
| --PATT | Pattern of Event | Char | AGE | Age | Num |
| --OUT | Outcome of Event | Char | AGETXT | Age Text | Char |
| --SCAN | Involves Cancer | Char | AGEU | Age Units | Char |
| --SCONG | Congenital Anomaly or Birth Defect | Char | SEX | Sex | Char |

| | | | | | |
|---|---|---|---|---|---|
| --SDISAB | Persist or Signif Disability/Incapacity | Char | RACE | Race | Char |
| --SDTH | Results in Death | Char | ETHNIC | Ethnicity | Char |
| --SHOSP | Requires or Prolongs Hospitalization | Char | SPECIES | Species | Char |
| --SLIFE | Is Life Threatening | Char | STRAIN | Strain/Substrain | Char |
| --SOD | Occurred with Overdose | Char | SBSTRAIN | Strain/Substrain Details | Char |
| --SMIE | Other Medically Important Serious Event | Char | ARMCD | Planned Arm Code | Char |
| --CONTRT | Concomitant or Additional Trtmnt Given | Char | ARM | Description of Planned Arm | Char |
| --TOX | Toxicity | Char | ACTARMCD | Actual Arm Code | Char |
| --TOXGR | Toxicity Grade | Char | ACTARM | Description of Actual Arm | Char |
| The Findings Observation Class | | | SETCD | Set Code | Char |
| **Variable Name** | **Variable Label** | **Type** | COUNTRY | Country | Char |
| **Topic Variable** | | | **Timing Variables** | | |
| --TESTCD | Short Name of Measurement, Test or Examination | Char | DMDTC | Date/Time of Collection | Char |
| **Qualifier Variables** | | | DMDY | Study Day of Collection | Num |
| --TEST | Name of Measurement, Test or Examination | Char | The Comments Domain | | |
| --MODIFY | Modified Term | Char | **Variable Name** | **Variable Label** | **Type** |
| --TSTDTL | Measurement, Test or Examination Detail | Char | STUDYID | Study Identifier | Char |
| --CAT | Category | Char | DOMAIN | Domain Abbreviation | Char |
| --SCAT | Subcategory | Char | RDOMAIN | Related Domain Abbreviation | Char |
| --POS | Position of Subject During Observation | Char | USUBJID | Unique Subject Identifier | Char |
| --BODSYS | Body System or Organ Class | Char | POOLID | Pool Identifier | Char |
| --ORRES | Result or Finding in Original Units | Char | COSEQ | Sequence Number | Num |
| --ORRESU | Original Units | Char | IDVAR | Identifying Variable | Char |
| --ORNRLO | Normal Range Lower Limit-Original Units | Char | IDVARVAL | Identifying Variable Value | Char |
| --ORNRHI | Normal Range Upper Limit-Original Units | Char | COREF | Comment Reference | Char |
| --STRESC | Result or Finding in Standard Format | Char | COVAL | Comment | Char |

| | | | | | |
|---|---|---|---|---|---|
| --STRESN | Numeric Result/Finding in Standard Units | Num | COEVAL | Evaluator | Char |
| --STRESU | Standard Units | Char | CODTC | Date/Time of Comment | Char |
| --STNRLO | Normal Range Lower Limit-Standard Units | Num | The Subject Elements Table | | |
| --STNRHI | Normal Range Upper Limit-Standard Units | Num | **Variable Name** | **Variable Label** | **Type** |
| --STNRC | Normal Range for Character Results | Char | STUDYID | Study Identifier | Char |
| --NRIND | Normal/Reference Range Indicator | Char | DOMAIN | Domain Abbreviation | Char |
| --RESCAT | Result Category | Char | USUBJID | Unique Subject Identifier | Char |
| --STAT | Completion Status | Char | SESEQ | Sequence Number | Num |
| --REASND | Reason Not Done | Char | **Topic Variable** | | |
| --XFN | External File Path | Char | ETCD | Element Code | Char |
| --NAM | Laboratory/Vendor Name | Char | **Qualifier Variables** | | |
| --LOINC | LOINC Code | Char | ELEMENT | Description of Element | Char |
| --SPEC | Specimen Material Type | Char | **Timing Variables** | | |
| --ANTREG | Anatomical Region | Char | SESTDTC | Start Date/Time of Element | Char |
| --SPCCND | Specimen Condition | Char | SEENDTC | End Date/Time of Element | Char |
| --SPCUFL | Specimen Usability for the Test | Char | TAETORD | Planned Order of Element within Arm | Num |
| --LOC | Location Used for the Measurement | Char | EPOCH | Epoch | Char |
| --LAT | Laterality | Char | **Qualifier Variables** | | |
| --DIR | Directionality | Char | SEUPDES | Description of Unplanned Element | Char |
| --PORTOT | Portion or Totality | Char | The Subject Visits Table | | |
| --METHOD | Method of Test or Examination | Char | **Variable Name** | **Variable Label** | **Type** |
| --RUNID | Run ID | Char | STUDYID | Study Identifier | Char |
| --ANMETH | Analysis Method | Char | DOMAIN | Domain Abbreviation | Char |
| --LEAD | Lead Identified to Collect Measurements | Char | USUBJID | Unique Subject Identifier | Char |
| --CSTATE | Consciousness State | Char | **Topic Variable** | | |
| --BLFL | Baseline Flag | Char | VISITNUM | Visit Number | Num |
| --FAST | Fasting Status | Char | **Timing Variables** | | |

| | | | | | |
|---|---|---|---|---|---|
| --DRVFL | Derived Flag | Char | VISIT | Visit Name | Char |
| --EVAL | Evaluator | Char | VISITDY | Planned Study Day of Visit | Num |
| --EVALID | Evaluator Identifier | Char | SVSTDTC | Start Date/Time of Visit | Char |
| --ACPTFL | Accepted Record Flag | Char | SVENDTC | End Date/Time of Visit | Char |
| --TOX | Toxicity | Char | SVSTDY | Study Day of Start of Visit | Num |
| | | | SVENDY | Study Day of End of Visit | Num |
| | | | **Qualifier Variables** | | |
| | | | SVUPDES | Description of Unplanned Visit | Char |

## APPENDIX 4 – PPB Processes Numbering Convention

| No. | Processes | Directorate/Department/Unit |
|---|---|---|
| 1 | **Pharmacy Profession Development and Practice regulation** | |
| 1.1 | **PROFESSIONAL CAPACITY DEVELOPMENT & MONITORING** | |
| 1.1.1 | Application for Indexing | Pharmacy Practice |
| 1.1.2 | Application for update of qualifications & personal details | Pharmacy Practice |
| 1.1.3 | Application to sit professional Exams | Pharmacy Practice |
| 1.1.4 | Application for letter of Internship placement | Pharmacy Practice |
| 1.1.5 | Application for Admission to Practice | Pharmacy Practice |
| 1.1.6 | Confirmation of CPD points/Examination Results | Pharmacy Practice |
| 1.1.7 | Professionals Movement reporting | Pharmacy Practice |
| 1.2 | **TRAINING INSTITUTIONS, PROGRAMMES & EXAMS** | Pharmacy Practice |
| 1.2.1 | Application for registration of Training Institution | Pharmacy Practice |
| 1.2.2 | Registration of Training programmes | Pharmacy Practice |
| 1.2.3 | CPD/Training Programmes Scheduling | Pharmacy Practice |
| 1.2.4 | Appointment of Examiners | Pharmacy Practice |
| 1.2.5 | Administration of Professional Exams | Pharmacy Practice |
| 1.3 | **PRACTICE REGULATION** | Pharmacy Practice |
| 1.3.1 | Practice License Application | Pharmacy Practice |
| 2 | **Products Regulation** | |
| 2.1 | **PRODUCT LICENSING & CERTIFICATION** | Product Registration |
| 2.1.1 | Application for registration of a Product | Product Registration |
| 2.1.2 | Application for Product compliance Certificate | Product Registration |
| 2.2 | **ANALYSIS AND QUALITY CONTROL** | Product Registration |
| 2.2.1 | Application for registration of clinical trials | Product Registration |
| 2.2.2 | Application for promotional material | Product Registration |

| | | |
|---|---|---|
| **2.2.3** | Products performance Reports | Product Registration |
| **2.2.4** | Post marketing survey of Drugs | Product Registration |
| **3** | **Pharmacy Trade facilitation** | |
| **3.1** | **BUSINESS LICENSING** | |
| **3.1.1** | Application for Pharmaceutical Business License | Pharmacy Practice |
| **3.2** | **IMPORT/EXPORT FACILITATION** | |
| **3.2.1** | Application for permit to export/import | Trade Affairs |
| **3.2.2** | Import/Export verification | Ports of Entry |
| **4** | **Enforcement** | |
| **4.1** | **INFORMATION** | |
| **4.1.1** | Consumption reporting | Inspectorate |
| **4.1.2** | Sensitization | Public Relations |
| **4.1.3** | Information exchange | ICT |
| **4.2** | **OTHER** | |
| **4.2.1** | Inspection | Inspectorate/Factory Audit |
| **4.2.2** | Service delivery reports | Inspectorate |
| **4.2.3** | Regulatory /Disciplinary Action | Inspectorate |
| **4.2.4** | Product recall and withdraw | Product Registration/Inspectorate/PV/Med. Info |
| **4.2.5** | Application for product Destruction | Inspectorate |