CHAPTER 1

INTRODUCTION

Clinical Data Management (CDM) is of critical importance in the drug development process and outcome of a clinical trial. Clinical trials, biomedical research studies on human subjects are done under strict ethical and regulatory framework. The data generated from a clinical trial serve to draw scientific inference, therapeutic or prophylactic spectrum, and as evidence that an investigational product is safe and effective for use in human [1]. Data, the clinical information gathered from a trial, is the most valuable information and its handling and management is the most critical step of a clinical study. CDM group keeps the database ready so that the clinical information collected could be entered into the database [2]. Poor management of data may lead to misleading outcomes. Irrespective of the big investment of time, resources, money and efforts for the conduct of the trial, if the quality of data is not as per the required standards, a meaningful analysis of study outcome may not be possible [3]. Conduct of Clinical Research industry is confronted with a multitude of regulatory constraints. Thus, regulatory requirements have advanced the necessity of CDM as science. Therefore the processes used to support the clinical data must be clearly defined and documented [4]. Over the last decade the global clinical research industry has attempted to work toward a common data standards with the goal of accelerating the drug development process by improving the data collection, transformation, analysis and submission [5]. Currently the World Health Organization (WHO) has the following guidelines and requirements that are relevant to the evaluation of vaccines: Good Clinical Practice (GCP) for trials on pharmaceuticals products, Good Manufacturing Practice (GMP) for pharmaceuticals, GMP for biologicals, regulation and licensing of biological products in countries with newly developing regulatory authorities, and guidelines form national authorities on quality assurance for biological products. Guidelines and recommendations for the production and control of specific vaccines are reviewed in detail in a series of WHO technical reports. However, there is no WHO document in the publically available literature to my knowledge that provides guidelines or standards for CDM conduct including planning [6], and data formats for the standardized representation of data and process implementation. It is recommended that the practice of CDM should be grounded to Good Clinical Practice (GCP);
overall the steps adopted for CDM should adhere to principles of good trial design and practices.

In India, there are two major guidelines which govern trial conduct assuring the ethical and scientific integrity. Indian GCP by CDSCO (Central Drugs Standard Control Organization) [7], [8], and ICMR (Indian Council of Medical Research) ethical Guidelines for Biomedical Research on Human Subjects [9]. These regulatory guidelines demand accurate, reliable and credible data but provide no explicit recommendations on how to adapt them for CDM processes. The focus of Indian regulatory is more on the site management, clinical trial operations, trial ethics governance and pharmacovigilance (safety data). However, there is no regulatory document that gives step by step clarity on procedures which may be adopted for CDM of drug or vaccine trials. It is the responsibility of the organization to identify, adapt to GCP, implement and document the processes so as to generate regulatory compliant data. There exists a great diversity in the procedure adopted for data processing and handling in the industry. The provisional CDM processes/criteria adopted are broadly based on opinion of experts. Arguably, there is no universal set of GCP standards or application of GCP principles, with variation in their implementation and applicable stringency of regulatory agencies. However, having no standardized CDM procedures, variations in procedures adaptation/operating guidelines practices and thereby differences in outcomes, may affect inference from clinical trials and compromise both quality assurance and regulatory compliance. Depending upon the phase of study and investigational product, specific set of clinical data management activities are needed.

A vaccine trial aims at establishing, not limited to the following, immunogenicity, reactogenicity, tolerability, safety, and efficacy prior to vaccine being licensed. Vaccine trials are different from other clinical studies as they are done on healthy subjects, and addressed, in particular, pediatric segment. This demands a very low tolerance for adverse event and compliance with high levels of ICH-GCP (International Conference on Harmonization published Good Clinical Practice) and other global regulatory agencies standards such as US-FDA (United States, Food and Drug Administration), EMEA (European Medicines Agency) and WHO, apart from national regulatory agencies before its market approval. Thus generation of quality data is of critical importance. As mandatory by Indian GCP, once the required data is generated and brought for processing, it has to be handled in a manner so that
it is complete, accurate, reliable and validated. Therefore, the role of CDM has become an essential component for vaccine development. The safety concerns and effectiveness of specific health and medical products and practices differ between countries and hence national governments regulatory norms/industry must accommodate (harmonize) them when committing to global standards. The un-harmonized national and international standards increase the cost of doing business apart from other hurdles. The global face of drug development demands that both government and industry pay more attention to internationally acceptable technical standards and conformance tests. In today’s competitive world, Indian Pharmaceutical companies, as true globally, are striving hard to streamline its internal procedures so that the time needed for its research related obligatory regulatory requirements can be drastically reduced with almost no hurdles for the product to reach market. These procedures must be established in such a way so that every time when the company wants to launch the product in a country different than that of its origin, the regulatory authorities of the new place must accept its original work, and as far as possible, must not mandate the company to do the task again, only because there have been gaps with respect to the implementation of the logical steps. Thus all the processes, steps and procedures adopted must always be in a way to satisfy demanding legislation, rules and regulations [10], [11].

There is a need that the data format should be standardized and the protocol/Data Management Plan (DMP) should provide clear guidance about CDM procedure implementation. Methods of assessing standardization or definition of standardization criteria and the design considerations to be applied in CDM, or operational benefits should be defined in protocols/DMP/ study reports and must be validated through audits. A recent report has highlighted regulatory non-compliance as a major issue among Indian life sciences companies; gaps exist pertaining to data management and quality control practices (GCP), apart from others (GMP, (GMP, Good Laboratory Practice (GLP)) [12]. Development of robust CDM procedures and implementation plans with assessable endpoints are the urgent unmet clinical/regulatory needs of Indian Pharmaceutical/Biopharmaceutical industry.
1.1 Purpose of Study: CDM Standardization in the context of vaccine trials in an Indian Pharmaceutical company

Framework that might emerge from establishing CDM procedural paths could improve clinical data management practices and thereby supporting regulatory compliance. India is fast becoming hub for vaccine research and development. Efficient and quality clinical data management remains a challenge. Effective CDM not only support consistent performance desired to meet increasingly tough and an inherently dynamic regulatory compliance requirements but it also drives all stages of drug development economics both prior to and subsequent to product registration and marketing, addressing key challenges not limited to the following. 1) mitigation of different types of error in the data, 2) support statistical analysis, 3) fast regulatory approvals, 4) assist in marketing the drug, 5) adaptability and easy redeployment of the CDM processes, 6) fast study site training, 7) procedural risk management, 8) elimination management of technical/procedural hurdles, 9) consistent and desired quality, 10) no need for database ‘unlocking’, 11) prevent duplication of tasks or redo trial and 12) identification of fraudulent data and malpractices.

A recent study in Europe showed that heterogeneity prevails [13] as there is no common standardized and validated global/national industry-wide CDM procedural and implementation framework. Such clinical scales are also the need for regulatory review to aid in drug development procedures as per GCP. Standardized CDM definitions, the process of developing and implementing technical standards, CDM data formats are needed to optimize data management. There are concerted efforts in the pharmaceutical industry to adopt a common data standard in various aspects of clinical studies and product development, for example, CDISC (standards for the interchange of clinical, non-clinical, laboratory, and statistical data) and GMP. However, a widely adopted common CDM procedural standardization/harmonization does not exist. A survey across Indian industry by the thesis author (described in Chapter 3) revealed that heterogeneity in CDM procedures exists suggesting a need for standard CDM procedural and implementation steps meeting the requirements of audits and/or inspections, and facilitating increasingly stringent and complex regulatory approvals.
1.2 Aims and Objectives

The aims and objectives of this study were to interpret, implement and standardize CDM procedures in a manner to support data output as needed by Indian GCP, meeting audit requirements and thereby enabling regulatory compliance, for vaccine studies conducted at Panacea Biotec Ltd., India. It is envisaged to set the stage for much needed progress in the establishment of procedures that might be used for the mapping of procedural path and evaluation that could facilitate regulatory submission and support review for market approval. Standardization shall help to develop a business solution which is process dependent, platform independent, vender neutral, transparent and devoid of duplication. This may also mean reduced training time, and flawless transmission of information between partners, providers and regulatory authorities [14]. Moreover, the lessons gained, if applied at the project commencement stage, may be helpful to improve the study design, conduct, documentation, reporting and interpretation by serving as a blueprint for forecasting project performance.

Objectives:

1. Define (interpretation) and implement CDM procedural steps based on industry prevalent best practices in the context of vaccine clinical trial (Myfive<sup>TM</sup> vaccine) in an Indian Pharmaceutical company, within the scope of Indian GCP regulations.

2. Documentation of CDM procedural steps in an effective manner to comply with audit requirements, to ensure procedural implementation so as to have quality data, with expected outcome that:
   - there are no major/critical findings with no SOP deviations,
   - no need to unlock database so that the data are adequately safeguarded
   - procedural steps suffice, operating in conformance with desired practices, to achieve the data quality expected by Indian GCP validated by QA (Quality Assurance Department).

3. Replication of audited CDM procedural steps to NUCOVAC® vaccine trial to achieve standardization
The objectives were enumerated through surveys (internal and industry feedback), to check the feasibility of the CDM processes based on the CDM parameters not limited to the following [15]:

- Compliance to Regulatory
- Quality for very small quantity of Data
- Quality for large quantity of Data
- Randomization & Blinding
- Support to multi-arms study
- Subject Confidentiality maintained
- Double Data Entry
- Data access by authorized person
- Data security system maintained
- Recorded audit trail
- Hardware & software – validation, adequate backup
- Credibility of the data based on the study design
- Data discrepancies handling

Quality Control (QC) activities; QC measures including, but not limited to the following were applied [15]:

- QC Report of CRF annotation
- QC Report of Database Designing and Entry Screen Layout
- QC report of 1st and 2nd Pass Test Data Entry
- QC Report of Validation Procedures
- QC Report of View Definitions, View templates and Data Extraction
- QC Report of Subject Enrollment
- QC Report of MedDRA (Medical Dictionary for Regulatory Activities) Coding
- QC Report of Discrepancy Status in OC (Oracle Clinical)
- 100% QC of Critical Data Points
- 100% QC of Random sample size using $\sqrt{n+1}$
- QC Report of DCFs (Data Clarification Form)
The chapter that follows “Review of Literature” details CDM practices prevalent in industry. The chapter “Research Methodology” outlines approach adopted towards identification, definition, implementation and standardization of easy-to-follow and practical CDM procedures, validated by QA. Each task is explained in a stepwise manner for the following vaccines: Myfie\textsuperscript{TM} (DTwP-HepB-Hib) and NUCOVAC\textsuperscript{®} (Pneumococcal) manufactured by Panacea Biotec Ltd. Next is the chapter that describes the outcomes of implemented steps and operational reward that shall facilitate auditing and regulatory compliance. The chapter Future Prospects describes metrics for CDM developed as Next Practice; multi-factor metrics based performance monitoring of critical procedural steps having synergistic impact in boosting overall in-time progression of the project and meeting desired data quality [16], a way forward to manage increasingly complex and stringent landscape of regulatory compliance. It is acknowledged that the common specification may not be suited to the needs of a given investigational product; it is imperative to establish the functional specifications (based on product type- vaccines/ drugs or therapeutic segment) and scope of the common data standards. Adoption of standard has helped to reduced noise by eliminating operational errors/variations, unnecessary procedures; implement, maintain, and improve common doctrines/processes to achieve/ensure consistent data quality in reduced time. This not only lowered costs involved but also enhanced competitiveness. Biggest benefit of standardization of CDM steps was achieving data quality that not only satisfied the requirements of applicable statutes and regulations but also supported study outcome in terms of data efficacy and product safety.