CHAPTER I

Introduction to validation parameters of analytical chemistry
General Introduction

Analytical chemistry is a science close to physical chemistry, which is a branch of pure chemistry. The objective of analytical chemistry is essentially to develop and apply new methodology and instrumentation with the goal for providing information on the nature and composition of matter. Analytical chemistry also allows the determination of a compound's structure, either partially or totally, in samples of different complexity. Finally, part of the role of analytical chemistry is to provide an interpretation of the results obtained. The term analytical chemistry involves the analysis of chemical elements and the defined compounds derived from these.

The vast discipline of analytical chemistry has implications in all experimental sciences. Its study requires knowledge of many different areas. As a multidisciplinary science, also sometimes referred to as transferable, analytical chemistry uses many phenomena, which may be remote from chemistry in the usual sense, in order to provide results. Thus, modern chemical analysis is based on physico-chemical measurements obtained through the use of a variety of instruments, which have greatly benefited from the appearance of microcomputers.

Chemical analysis has become indispensable in many areas other than traditional chemistry or Para-chemistry. Chemical analysis is now used in the medical sciences (for treatment and diagnostics), in biochemistry, food chemistry, environmental sciences (pollution) and in numerous industrial areas. 95% of the pharmaceutical compounds are of synthetic origin. Pharmaceutical means drug in formulation i.e. the drug is not administered in its pure form, as was done earlier, but is administered as tablets, capsules, injections and syrups with several excipients. This means that methods of assay should be
compatible with the presence of excipients like lactose, starch etc. For the drug to be manufactured in pure form, it is important to keep a strict vigil on quality at all stages of its manufacture. For better quality assurance, it is necessary to start with raw materials that ensure the quality of the final product and obviate the necessity of determining the impurities in the final product. The impurities in the final product are confined to those arising from incomplete and side reactions, due to environmental condition (i.e. oxidation, reduction, hydrolysis etc). This has necessitated the development of organo-analytical chemistry, for not only the assay of a drug / chemical but also for determining its impurities profile. In pharmaceutical industry, prime importance is given to the quality of the drug which can be defined as the sum of all the factors which contribute directly or indirectly to the safety, efficacy and reliability of the product. Quality assurance in a pharmaceutical industry ensures that a product meets the requirements of the term, quality.

**Role of Pharmaceutical Industry**

Over the years, the pharmaceutical industry has played a vital role in human battle against diseases, disability and suffering at global level. For most part of this century, doctors and the drug industry have tried to prepare medicines in laboratories using synthetic chemicals and these provide more control over quality and quantities of their products. Safe and effective drug therapy, however, is possible only with strict observation of current Good Manufacturing Practice (cGMP) of drugs and careful quality monitoring of their active ingredients in pharmaceutical preparation and in bulk drugs. "Quality" and "Cost-effectiveness" are the buzzwords in today’s changed environment of globalised and liberalised economy and the only way to survive in this competitive world is by
maintaining a constant upgradation of quality. Quality is important in every product or service but it is vital in medicine which involves life. Unlike ordinary consumer goods, there is no "second" quality in drugs. Quality is the sum of all the factors which contribute directly or indirectly to the safety, efficacy or acceptability of the product.

The purpose of any manufacturer is to sell to a targeted customer, a right product at the right price with right quality aspects. In the case of pharmaceutical industry business, the right product is the one, in various dosage forms, which conforms to all its requirements in terms of physical, chemical and microbiological parameters throughout its shelf life. The functions responsible to achieve these objectives are defined as Quality control.

**Quality Control**

Quality as per the dictionary definition is the degree of excellence which a material possesses. Quality control is defined as the management function to control the quality of a product to a defined set of standards.

The quality control function in an organization which normally consists of at least two primary units includes

i) Analytical control and

ii) Inspection Control

Only after the production document review has been completed satisfactorily, the batch may be released for distribution. Government legislation in America and Britain in 70's brought about what is called as "Good Manufacturing Practice (GMP)". It can be defined as a set of detailed procedures during product manufacturing documentation of all relevant aspects encountered during manufacturing including quality control. In our country, GMP has been made statutory in 1988 and a set of guidelines to be followed
during manufacturing has been included, along with a near schedule called "Schedule M" in Drugs and cosmetic Acts and Rules. Thus, the testing of raw materials and finished products gave way to details in process check during manufacturing and compliance to GMP. There has been more assurance of product quality in the last two decades than mere control of the 60s and the department was renamed as “Quality Assurance” department, in place of “Quality Control “department.

Quality Assurance

Normally, standard operating procedures (SOPs) are developed, which when followed by properly trained operators, will help to assure the quality and integrity of the product. In recent years ISO 9001 certification and USFDA approval has become very important for the export of the drugs. ISO 9001 is a Quality Audit System. It follows very simple principle “Write what you do and do what you write ”. Thus the quality management can be simply defined as a function which is concerned with preventing problems from occurring by creating the right attitudes and controls.

In today's context, the emphasis of a GMP demands a zero defective approach to pharmaceutical preparations and in bulk drug productions. There must be the will to produce superior quality product. To maintain the quality of drugs and pharmaceutical products, it is essential that quality assurance department should adopt “Current Good laboratory Practice”.

Good Laboratory Practice

In practice the quality of medicines or pharmaceutical products is assured through quality control. It is therefore essential that the quality assurance department adopts “Good Laboratory Practice “to ensure reliability and accuracy of the results given out by
them. The assurance of the quality and the reliability of pharmaceuticals, together with their careful control are our moral obligations.

Attainment of this quality objective requires involvement and commitment of all concerned at all stages. All these efforts taken by an organization with respect to Quality Assurance, Good Manufacturing Practice and Quality Control, lead us to better quality and acceptability of the product. Following analytical techniques have been employed for estimation of different components in formulations.

1. Volumetric and Gravimetric
2. Ultraviolet and Visible adsorption Spectrophotometry
3. High Performance thin layer chromatography (HPTLC)
4. Gas Chromatography (GC)
5. High Performance Liquid Chromatography (HPLC)
6. Paper chromatography
7. Ion exchange chromatography

Among these methods, chromatographic techniques are receiving great importance and popularity in growth, utility and applications. In the present work, HPLC technique has been chosen for the development of analytical methods for some drug formulations. The methods developed for pure forms were successfully employed for quantitative evaluation of the drugs in their respective available pharmaceutical preparations in view of their validation and utility in Quality Assurance.

**Analytical Procedure Validation**

The efficacy and safety of a medical product can be assured by analytical monitoring of its quality. Therefore, the overall purity of a medicine must be assessed throughout its storage, distribution and use. This objective can possibly be achieved if the
specifications to be applied are based on a validated procedure. It is therefore imperative that, any analytical procedure proposed for analysis of a particular active ingredient or its dosage form, be systematically evaluated so as to demonstrate that the method is scientifically sound under the conditions in which it is to be applied. The purpose of analytical validation is to ensure that the proposed analytical procedure under consideration is capable of giving reproducible and reliable results. The following parameters are checked in method validation.

**Specificity and interference:**

While carrying out the particular test procedure in the prescribed manner, the analyst assumes that the results of the test refer only to the active ingredients in the sample matrix under analysis. Sample matrix may contain impurities arising from manufacturer or degradation related chemical components or placebo ingredients. Specificity is a measure of the degree of interference in the analysis of complex sample mixtures.

**Accuracy**

Accuracy of the procedure relates to the closeness of the results obtained by the procedure to the true value. The accuracy of a test procedure can usually be determined by applying it to the quantitatively prepared samples of the material to be analysed and expressed as percent recovery by the assay of known amount of the analyte.
**Precision:**

The precision of the analytical methods relates to the degree of agreement among individual test results and how individual results are scattered from the mean value, usually expressed as, Relative Standard Deviation. Precision is a measure of the degree of reproducibility of the analytical method under normal circumstances.

**Reproducibility:**

When the procedure is carried out many times using the samples from same homogeneous batch, the analytical data provide information about the reproducibility of the test procedure under validation.

**Linearity and range:**

The Linearity of an analytical procedure is its ability to produce results that are directly or indirectly proportional to the concentration of analytes in the samples within a given range. The range of the procedure is an expression of the lowest and highest levels of analytes that the method can determine with reasonable accuracy and precision.

**Limit of detection:**

This is defined as the lowest concentration of substance in a sample that can be detected but not necessarily determined quantitatively under the stated experimental conditions. Generally, this is taken as three times the standard deviation of the blank solution (3S).
Limit of quantification:

This is defined as the lowest concentration of substance in a sample that can be determined quantitatively with acceptable accuracy and precision using the recommended procedure of analysis. Normally, this is calculated using the formula $10S$, where “$S$” is the standard deviation of the blank.

Ruggedness:

The ruggedness of the analytical method is defined as the ability of the procedure to provide analytical results of acceptable accuracy and precision. The ruggedness of the method takes into consideration, the variation that may be expected when a prescribed procedure of analysis is employed with different reagents and equipments.

Simplicity:

The analysis should be carried out in a minimum number of steps and needs only easily available reagents and equipments.

Time cycle:

It is the time taken to complete the analysis. Greater the number of steps involved, greater will be the time required to complete the analysis.
Cost of analysis:

The simplicity of the method, the number of steps involved, the time cycle, the availability and cost of reagents, the requirements of costly instruments, skilled and experienced analysts are major factors which contribute to the cost of analysis.
References


5. Gilbert, J; *Total Quality Management*.