HOW TO PRACTICE GLP

Third Edition

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PREFACE TO THIRD EDITION

When I authored the first edition of this book, there was no formal or informal text of Good Laboratory Practice (GLP) from the regulatory authority in India. Therefore, the guidelines appearing under the US FDA GLP were the basis for how to guidelines in the first edition of this book. Some developments have taken place since then. A sub-committee of the Drugs Consultative Committee brought out the guidelines for GLP. These guidelines were published by the Central Drugs Standards Control Organization (CDSCO). Later, the Government of India published draft rules incorporating Schedule L-1 under the Drugs & Cosmetics Rules. These draft rules were made the basis of discussion in the second edition of this book along with OECD and US FDA GLP.

The Government of India, Ministry of Health & Family Welfare published final amendment to the Drugs & Cosmetics Rules in November 2008 with stipulation that the provisions of the amendment will be effective from 1st November, 2010. Since, these amendments are now part of the Drugs & Cosmetics Rules, the basis of discussion of GLP guidelines in this edition is based on Schedule L-1. However, wherever necessary, a reference to similarity or otherwise has also been made to the OECD or US FDA GLP guidelines.

At one time, it was being contemplated by the CDSCO that NABL accreditation will be made mandatory to the drug testing laboratories in India. But it has not been done so far.

There are certain procurement agencies for drugs which get their samples tested at drug testing laboratories. These agencies insist that drug testing laboratory should be NABL accredited. Therefore, a chapter has been added on NABL accreditation.

OECD countries require safety data on chemicals, drugs, cosmetics, veterinary drugs, food additives etc. from OECD GLP compliant testing laboratories, if such items are imported into those countries. The Government of India, Ministry of Science & Technology, has established the National GLP Compliance Monitoring Authority under the aegis of Department of Science &

Technology. This authority issues GLP compliance certificate for the compliance of OECD GLP principles. Therefore, a chapter has been added on GLP certification. This will be useful to those drug manufacturers which export drugs to the OECD countries.

On technical side, calibration and qualification of instruments is very important. Reliable and consistent analytical data can not be obtained without these activities. Therefore, a chapter has been added on calibration and qualification of analytical instruments.

The book will be useful to quanlity control chemists, QA personnel, regulatory officers, pharmacy faculty and students, and consultants.

I am thankful to all those who helped me in collecting information and to those who helped me in bringing out this edition. I look forward to similar cooperation and help in future also.

January, 2012 **P.P. Sharma**

PREFACE TO FIRST EDITION

A Consumer will like to have a drug of quality, purity & efficacy and will also like it to be safe. A manufacturer of drug can not give assurance to the above unless he has tested the drug for the said parameters. The testing of drug can be carried out either in the manufacturer's own testing laboratory if it is adequately equipped or in an approved testing laboratory. GLP is a quality system for testing laboratory. Implementation of GLP will result in reliable data.

Although US FDA GLP are applicable to non-clinical laboratory studies that support or are intended to support application for research or marketing permits for products regulated by the Food and Drug Administration, but many elements of these GLP are of universal application. Therefore, US FDA GLP elements have been discussed in the book with their relevance in India.

There are two important functions every testing laboratory will be involved in viz. (i) inspection & test, (ii) sampling. Therefore, these two topics have been included in the text of the book. Statistical quality control (SQC) is a powerful tool for process control. Quality control staff of the drug manufacturers will find a chapter on SQC very useful. Health and safety is an important aspect irrespective of the fact that whether testing laboratory is a part of industrial unit or it is an independent laboratory. Therefore, a chapter has been included on laboratory safety.

To understand quality assurance fully, some terms related to quality are required to be understood. An effort has been made to explain the terms related to quality in the very first chapter of the book.

There is no Indian book on GLP relevant to pharmaceutical industry. I have made an effort by writing this book on the subject. Being a maiden effort, it may have some imperfections. I will look forward to the readers and critics to give me feed back, so that I make amends in the future.

I am thankful to all those who have helped me in collecting the material on different topics. I am also thankful to Paragon Computers who composed the text and Rakmo Press Pvt. Ltd. who printed the book.

January, 2000 **P.P. Sharma**

CONTENTS

Introduction

Like the evolution GMP, there is history and evolution of Good Laboratory Practice (GLP) also. Singer and Upton[1] in the book, Guidelines for Laboratory Quality Auditing have given an account of GLP when it was first published in Federal Register of USA. Comments received, their analysis and the Commissioner, US FDA's decisions have also been mentioned in the book. Prior to publication of GLP, what had happened? It was found by the FDA that some studies submitted in support of the safety of regulated products had not been conducted in accordance with acceptable practice. Data from studies could not be considered of a quality and integrity to assure quality and integrity to ensure product safety under the Federal Food, Drug and Cosmetic Act and other applicable laws. In view of this, FDA prepared GLP as Part 3e in Title 21 of the Central Federal Regulations (CFR). Later on, this section was changed to Section 58. Currently it is CFR 21 Part 58.

These regulations were the first of a series of regulations concerning investigational requirements which were developed as a result of the FDA Bioresearch Monitoring Program. The proposed regulations were published in the Federal Register of November 19, 1976 (41FR 51206). A period of 120 days was given to interested persons to submit comments. In addition to this, public hearings were held on February 15 & 16, 1977 for the presentation of oral testimony on the proposal. Twenty two oral presentations were given and 174 written comments were received. All these were considered and some amendments were made based on the representations & comments. The final rule incorporated them into a new Part 58 (21 CFR 58).

Different products regulated by the agency for which safety data may be required cover a wide range. Examples include:

- implantable medical devices;
- indirect food additives which may occur in food in very small quantities;
- direct food additives which may be consumed daily in larger quantities;
- human drugs intended for prescription or over the counter use;
- animal drugs intended for use in pets and other animals of social importance;
- drugs used in food producing animals,
- radiation products used in the diagnosis and/or treatment of a disease or condition;
- radiation products (microwave ovens and television sets) widely used by public;
- vaccines;
- blood products.

Now a days, in India, there are companies which have multi-site operations including USA. Also readers may be interested to go through the text of US FDA GLP. Therefore, the text of US FDA GLP is being reproduced as Appendix I of this book.

Based on US FDA GLP, the Organization for Economic Cooperation and Development (OECD) also developed GLP. OECD is an intergovernmental organization of 29 industrialized countries in North America, Europe and the Pacific. The Singer & Upton[2] in the book mentioned above also describe the development of the OECD GLP. Chemical control laws were passed in many member countries. The laws required testing and assessing of chemicals to determine their potential hazards. The underlying principle of these legislations was that assessment of hazards associated with chemicals should be based on data of assured quality. Good laboratory practice is intended to promote the quality and validity of data. GLP has been defined as the quality system concerned with organizational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported under the OECD series on principles of Good Laboratory Practice & Compliance Monitoring, Number 1[3].

Application of GLP is of importance to national authorities which have been entrusted with responsibility of assessing test

data and evaluating chemical hazards. If the countries can rely on the test data developed in other countries, duplication of studies can be avoided and this would result in cost saving both to the industry and government. Secondly, common principles and procedures of GLP facilitate exchange of information.

The OECD Principles of Good Laboratory Practice were developed by an expert committee on GLP established in 1978 under the special program on the control of chemicals. US FDA GLP developed by then made the basis for the work by the committee. The committee was headed by Dr. Carl Morris of US Environmental Protection Agency. The OECD Principles of GLP were first published in 1982 as Good Laboratory Practice in Testing of Chemicals. This publication also contained guidance provided in the final report of the Expert Group. Since then OECD has been continuously refining this guidance. The results of this effort were published in the OECD Series on Good Laboratory Practice and Compliance Monitoring beginning in 1991. The current version, OECD Series on Principles & Good Laboratory Practice and Compliance Monitoring, Number 1 (OECD Principles on Good Laboratory Practice was revised in 1997). In this series, several guides have been published. These are given in Appendix II.

A number of countries for import of several items like industrial chemicals, pharmaceuticals, veterinary drugs, pesticides cosmetics, food products, feed additives require the manufacturers of above mentioned items to establish through data that use of these products do not pose hazards to human beings and the environment. Nonhazardous nature is required to be established through studies. The data generated during these studies is examined by the regulatory authorities of the importing countries.

India, at present, enjoys the status of provisional member of the OECD for GLP. Head, National GLP Program has been nominated by the Dept. of Science & Technology, as an observer to the OEDC's Working Group on GLP. He is also National Coordinator for OECD's Test Guidelines Program. India is making efforts to get status of full membership.

In pursuance of this, a National GLP Compliance Monitoring Authority has been established by the Department of Science & Technology (DST), Government of India[4].

The National GLP Program functions through an Apex Body with Secretary, DST as its Chairman and Secretaries of concerned Ministries/Department, Director General, CSIR and Drugs Controller General (India) as its members. The Apex Body is responsible for ensuring functioning of National GLP program according to the OECD principles. The Apex Body is supported by Technical Committee on GLP, National Coordination Committee for OECD Test Guidelines Programme and Legislation Committee to enact a National Legislation on GLP. National GLP Compliance Monitoring Authority has published following documents.

Information Brochure	: (GLP 100)
Terms and Conditions	: (GLP 101)
Application Form	: (GLP 102)
Requirements for Test Facilities	: OECD Principals of Good Laboratory Practice

The National GLP Compliance Monitoring Authority issues GLP Compliance Certificate. GLP Compliance Certification is voluntary in nature. The testing laboratories have to apply in prescribed application form. Following the application, inspection of testing laboratories is carried out by the GLP inspectors. The first inspection is pre-inspection of the laboratory. It is followed by final or second inspection. The report of the GLP inspectors is put up to the Technical Committee for recommendation to the Chairman, National GLP Compliance Monitoring Authority. GLP Compliance Certificate once issued is valid for three years with annual surveillance and a reassessment during the third year. For more information, readers may refer to the website: http://www.indianglp.gov.in and Chapter 10 of this book. Considering the importance of the OECD GLP in Indian context as many bulk drugs are being exported to including OECD countries, the elements of OECD GLP have been reproduced in Appendix III. Full text of OECD GLP is available on the website of the National GLP Compliance Monitoring Authority and also on the website of the OECD.

Earlier there were no GLP guidelines under the Drugs & Cosmetics Rules. However, there were certain provisions under the rules which were in line with GLP requirements. Subsequently, the Central Drugs Standards Control Organization (CDSCO), under the Directorate General of Health Services, Ministry of

Health & Family Welfare, Government of India prepared Good Laboratory Practice Guidelines for Drug Testing Laboratories in India. These guidelines were prepared by a sub-committee constituted in the 32nd Meeting of the Drugs Consultative Committee (DCC). After a couple of years, Dr. Mashelkar Committee made recommendations to include GLP under the rules. The Ministry of Health & Family Welfare, Government of India notified draft GLP Guidelines as Schedule L-I of the Drugs & Cosmetics Rules in October 2006[5]. After a gap of two years final amendment was made under the Drugs & Cosmetics Rules, 1945 and the amendment was notified vide G.S.R.780(E) dated 10th November, 2008 with the stipulation that these rules would come into force from 1st November, 2010. As such, GLP prescribed under Schedule L-I are a part of the rules now. The notification has been reproduced as Appendix IV in this book.

When the author wrote the first edition of this book, no national GLP Guidelines were available. At that time even National GLP Compliance Monitoring Authority was also not established. As such, the discussion for practice of GLP was mainly based on US FDA GLP and the provisions of the Drugs & Cosmetics Rules. Since now the GLP Guidelines have been notified and have become a part of the Drugs & Cosmetics Rules, the Schedule L-I has been made the basis of discussion in Chapter 8. References of equivalent or similar provisions under OECD GLP and US FDA GLP have been made.

The scope of three GLPs i.e. Indian GLP, OECD GLP and US FDA GLP is different. While the Indian GLP are required to be complied with by the testing laboratories attached to the drug manufacturing units and the approved testing laboratories under Part XV (A) of the Drugs & Cosmetics Rules, the scope of OECD GLP is to generate data to demonstrate that the items falling under the scope of these GLP are not hazardous to human beings or to the environment. Such data is requirement in OECD countries and therefore will be relevant to the exporters in India who want to export the items within the scope of the GLP to the OECD countries.

The scope of the US FDA GLP is conducting studies (non-clinical) to support or intended to support applications for research or marketing permits for products regulated by the Food & Drug Administration including food and colour additives,

human and animal drugs, medical devices for human use, biological products and electronic products. Some manufacturers of bulk drugs are now exporting their products to US and therefore, US FDA GLP will be relevant to such manufacturers.

References

1. Singer, D.C., Upton, R.P. Guidelines for Laboratory Quality Auditing, Marcel Dekker Inc. New York (1993), Appendix E.
2. Singer, D.C., Upton, R.P. Guidelines for Laboratory Quality Auditing, Marcel Dekker Inc. New York (1993), Appendix C.
3. OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, Number 1, Environment Directorate, OECD, Paris, 1998.
4. Website: http://www.indiaglp.gov.in/aboutus:htm
5. GSR 634 (E) dated 13.10.2006, Gazette of India.

Chapter 1

Quality and Related Terms – Basic Concepts

1. QUALITY

The term "*quality*" is used by people in day to day life frequently but most of the people, most of the time while using term, quality might have in mind one or the other property of a product or service. For example, some body buys a pen and when he uses it, he finds, it does not have uniform flow of ink. At that moment, when he says the quality of this pen is not good, he has in mind flow of ink. But in totality, he will like many more features (properties) in a pen e.g. it should be smooth in writing, it should not write too thick or too thin, it should be elegant in look, it should be so priced as is within his reach etc.

Now let us consider an example of a tablet for pain. The first and foremost property, a tablet for pain should have is to alleviate pain. Besides this, it should be elegant in appearance, good in taste and/or flavour, nicely packed, economically priced.

Thus it can be said that quality is customer's determination and not a producer's determination. It is based on the customer's experience with the product or service measured against his requirements. These requirements may be stated or unstated, conscious or merely sensed, technically operational or entirely subjective. From this, it can be stated that quality is not static in nature. Since it is related with the aspirations of user, quality is dynamic in nature and the aspirations of user prompt producer of goods to improve quality.

If a product or service responds to the overall requirements (needs) of consumers, a product or service is said to possess marketability or saleability. Among these overall needs, how best

the product serves the purpose of the user, during its usage, is called its "fitness for use". The other terms which have been used for this concept include, "fitness for purpose", "customer satisfaction", "conformance to requirements". The concept of fitness for use is universal and has been popularly called by the name of quality.

Before discussion on quality proceeds further, there are three terms which should be understood clearly. These are given below:

Customers, consumers & users: There are three different terms:

(i) customers
(ii) consumers and
(iii) users.

These are used, many a time, in confusing manner substituting one for the other. Therefore, it will be useful to understand them. A customer is one who buys or procures product from another. The purchase may be for the purpose of resale. In such a case, customer is commonly a type of merchant. The other type of purchase may be for use. In such a case, the customer is also an user. If it is a purchase of service, the purchaser is often termed client.

An user is one who receives the intended benefits of the product. The user may consume the product, for instance fuel for burning or he may further process it to make a different product for sale, for example, a drug manufacturer purchases bulk paracetamol and converts it into paracetamol tablets for sale. Individuals and families who consume products for personal purpose are commonly called consumers e.g. food, drugs, cosmetics.

To an economist, there are two different things: (i) product, for example, drugs, foods, automobiles and (ii) service, for instance, power supply, hair cutting; but the user is interested only in services even though he may seem buying products. When he buys drugs, he wants cure of ailment. When he buys milk, he wants nourishment. When he buys automobile, he wants transportation. The service industry, usually, sells service directly to consumers without intervention of merchants. On the contrary,

manufacturing companies, those in particular, who make consumer products sell through an intermediate chain of merchants. Thus the service industry gets direct feed back from consumers and becomes sensitized to the concept of "fitness for use". Product industry lacks in direct feed back, as such, it tends to emphasize conformance to the product specifications rather than fitness for use. Although fitness for use is judged by the user but it is specified by well known parameters. These parameters are quality characteristics.

1.1 Quality Characteristics

Any feature of the products, materials or processes that is needed for achieving fitness for use is a quality characteristic. The feature may be property, attribute etc. These characteristics may be of different kinds:

- Technological e.g. acidity, alkalinity, pharmacological activity;
- Psychological e.g. beauty, taste, smell
- Time oriented e.g. reliability, maintainability
- Contractual e.g. guarantee provisions
- Ethical e.g. courtesy of sales personnel

Though the concept of quality characteristics is as old as human beings themselves. However, it may not have been quantified in early age but were judged by experience. Technological characteristics were quantified even centuries ago with the advent of instruments. Now, with the development of science & technology, these are extensively quantified. Service industry quality characteristics also include the above mentioned quality characteristics, but are dominated by the psychological & ethical. In addition to the above, service industry regards promptness of services as quality characteristic. Manufacturing companies regard promptness as different parameter than quality. The distinction, sometimes, is so sharp that there is separate organization to set standards for delivery schedules – production control.

Quality characteristics can be classified into several categories or parameters of fitness for use. The classification helps to define more precisely the needs of the user and also helps in understanding of the major economic forces involved. The major

parameters are:

- quality of design;
- quality of conformance;
- the abilities;
- field service.

1.1.1 Quality of Design

All human beings have certain basic needs e.g. food, cloth, shelter. With growing industrialization, basic needs of society have also grown e.g. transportation, communication, besides these, human beings have powerful urge for control over forces of nature, for security, for comfort, for artistic achievements or for excellence in the field. While their wishes are endless, but purchasing power of human individuals or their organizations are variable. This variable level of purchasing power has led to creation or recognition of different levels of excellence of products and services. For example, transportation can be achieved through train, bus, private car or airplane. Each of these levels can be called grade. A difference in grade is a difference in quality of design. Grade is a non-technical term and is used widely. By the term, it is understood in public that it relates to a level of fitness for use and level of purchasing power. Quality of design is a technical term & it may be regarded as composite of three different steps in a common progression of activities:

- Identification of what constitutes fitness for use. There is no widely accepted term to describe this activity. Since identification of fitness for use is the result of market research, the effectiveness of this activity might be termed as "quality of market research". For example, a company carries out market research and finds out that there is a large market for anti-infectives.
- Selection of a concept of product or service to be responsive to the identified needs of the user. Different professionals in the field of quality have used different terms to designate the extent to which the intended features of the product respond to the actual market needs. Some of them are, "quality of concept", "quality of project", "quality of design". For example, the company found out potential market for anti-infectives. Now in the second step the

dosage form is to be selected whether it should be marketed as a tablet or capsule or injection.

- Translation of selected concepts into a detailed set of specifications. When it will be executed, it will meet the needs of the user. The term, "quality of specifications" has been used to describe the extent to which the actual design specifications conform to the needs for fitness for use for the grade. For example, specifications for selected dosage form. In case of drugs, help may be taken from pharmacopoeias which prescribe specifications for different dosage forms.

The total progression of these activities is usually called the "quality of design". Other terms which have been used in literature and may be seen as synonymous with quality of design include "degree of excellence", "design adequacy", "design capability" etc.

1.1.2 Quality of Conformance

The design of the product should reflect the needs of fitness for use and the product should also conform to the design. In the example chosen for illustration the anti-infective should have strong anti-infective activity so that patient is cured of infection. Besides this, it should meet the specifications for the chosen dosage form. Then extent to which the product conforms to the design is called the "quality of conformance". This term is widely used & accepted. Alternate terms which have been used in the literature are "quality of manufacture", "quality of production", "quality of product". Quality of conformance is dependent on numerous variables like machines, tools, supervision and workmanship.

1.1.3 The Abilities

For products which are consumed promptly after purchasing e.g. foods, medicines, fuels, two parameters, namely, "quality of design" and "quality of conformance" are largely sufficient to determine fitness for use. For products which are used over a long period e.g. fan, refrigerator, other factors come into play viz. availability, reliability and maintainability. These abilities are interrelated and are vital to fitness for use concept and have been discussed briefly in proceeding paragraphs.

(i) Availability – In today's industrialized society, continuity of life depends on the continuity of services from sources of energy, communication, transport, water etc. A lot of effort has been made to provide this continuity & to discover promptly when failure occurs. One element of this effort has been to recognize continuity of service as a parameter of fitness for use and to recognize continuity of services as a parameter of fitness for use and a facility to measure it. This parameter has been named as "availability". It is time related and it is measured by the extent to which the user can secure the services as and when he wants it. A product when it is in operative state is said to be available. The total time in operative state, also called as the up time is sum of the time spent in active use and the time in standby state. Similarly, the total time in non-operative state also called as downtime and it is the sum of the time spent under active repair and waiting for spare parts, authorization etc. Mathematically, availability can be expressed as:

$$\text{Availability} = \frac{\text{Uptime}}{\text{Uptime} + \text{Downtime}}$$

Availability can also be expressed by the ratio of mean time between failures (MTBF) and sum of MTBF plus mean time to repair (MTTR).

$$\text{Availability} = \frac{\text{MTBF}}{\text{MTBF} + \text{MTTR}}$$

Other terms which have been used as equivalent to availability are "operational readiness" and "percent uptime."

(ii) Reliability – If a product never failed, availability would be 100% for that product. But products fail. Therefore, an essential sub-parameter of availability is freedom from failure. The term, "reliability" has been used for this sub parameter. Classic definition of reliability is:

> *"The probability of a product performing without failure a specified function under given conditions for a specified period of time".*[1]

In general, reliability means the ability of a person, or system to perform and maintain its function in normal and hostile

conditions. The Institute of Electrical & Electronics Engineers (IEEE) defines it as "....the ability of a system or component to perform its registered function under stated conditions for specified period of time."

The probability of performing without failure can be converted to other measures like mean time between failures (MTBF), failure rate etc. For simple systems, the calculations are simple but for complex systems these become very complex. Reliability is determined, to a large extent, by quality of design. Attainable reliability which is inherent – in the design is called "intrinsic reliability". However during use, the achieved reliability is usually less than this because of unanticipated environments, lapses in quality conformance, inadequacies in maintenance etc.

Reliability should not be confused with conformance to product specifications or even with reliability estimates, which may be made, based on life tests in laboratory. Evaluation of achieved reliability requires collection and interpretation of data on performance and failure of a product while in actual use over a period of time.

(iii) Maintainability – The need of continuity of service has been emphasized in earlier paragraphs. This has stimulated efforts to improve maintenance of durable products. This maintenance may take place mainly in two ways.

- preventive or scheduled maintenance;
- unscheduled maintenance.

Preventive maintenance consists of tests and checks to detect potential failures, scheduled servicing and planned overhauls plus replacement of worn out or failure prone parts. Unscheduled maintenance consists, of restoring service in event of failure.

The term, "*maintainability*" has been used as an expression of the ease with which maintenance can be carried out. If we think of quantifying maintainability, we soon encounter the fact that multiple measures are involved as maintenance requires not only time but also manpower, spares, expendable supplies and other inputs. Of these measures, those which are time oriented are regarded as the most important as human activity is affected

until service is restored. The measures of maintainability which are in use are:

- mean time to repair (MTTR);
- probability of restoring service in time period specified;
- meantime for scheduled maintenance.

Effectiveness of maintenance is greatly influenced by various factors which include:

- design for easy access and modular replacement at the premises of the user;
- instruments for easy diagnosis of cause of failure;
- repair tools;
- technical information about the product & its use.

Effectiveness of maintenance is also influenced by the availability of spares sometimes, this is called "logistical support".

1.1.4 Field Service

The parameters which have been discussed in foregoing paragraphs are influenced mainly by what goes on prior to sale of the product. After the sale of the product to an user, the ability of the user to get continuity of service depends largely on service organization. The service organization is expected to carry out following functions:

- It should provide clear, unambiguous service contracts;
- It should establish stores of adequate repair equipment and spare parts;
- It should recruit & train service force to make them competent enough to diagnose & remedy failures;
- It should respond promptly to service calls;
- It should conduct its affairs with courtesy & integrity.

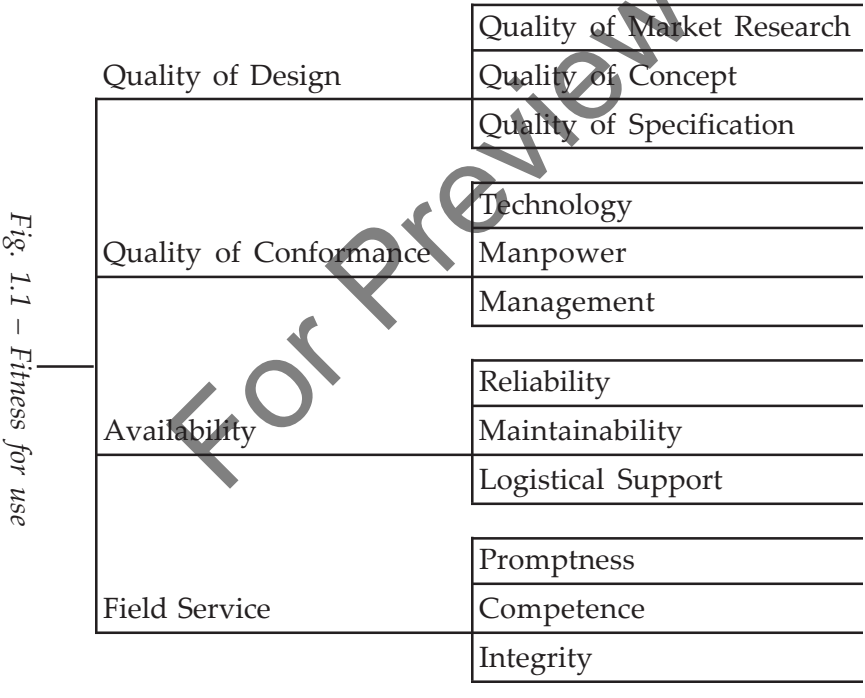
This parameter is known by different terms which include "field service", "customer service", "sales service" or just "service". The features which distinguish this parameter are:

- it relates to the activities which are carried out after sale;
- it is performed by an establishment which is regarded as service industry rather than manufacturing industry;
- it includes extensive contact with the user on account of contractual or informal obligations.

The above mentioned parameters can be sketched out in the form of a tree that helps in bringing out inter-relationship. There are several ways of subdividing these parameters, structuring the resulting trees and setting up models for evaluation. One such tree is shown in Fig. 1.1.

Quality is a subjective term and thus each person or sector has its own definition. However, technically quality can have two meanings:

- the characteristics of product/service which bear on its ability to satisfy stated or implied needs;
- a product/service free of deficiencies.



There are two very well known quality gurus, Joseph Juran and Philip Crosby. According to Juran, quality means "fitness for use" and according to Crosby, quality means "conformance to requirements".

2. QUALITY FUNCTION

An organization which produces & markets its products or provides services does it through a series of specialized activities

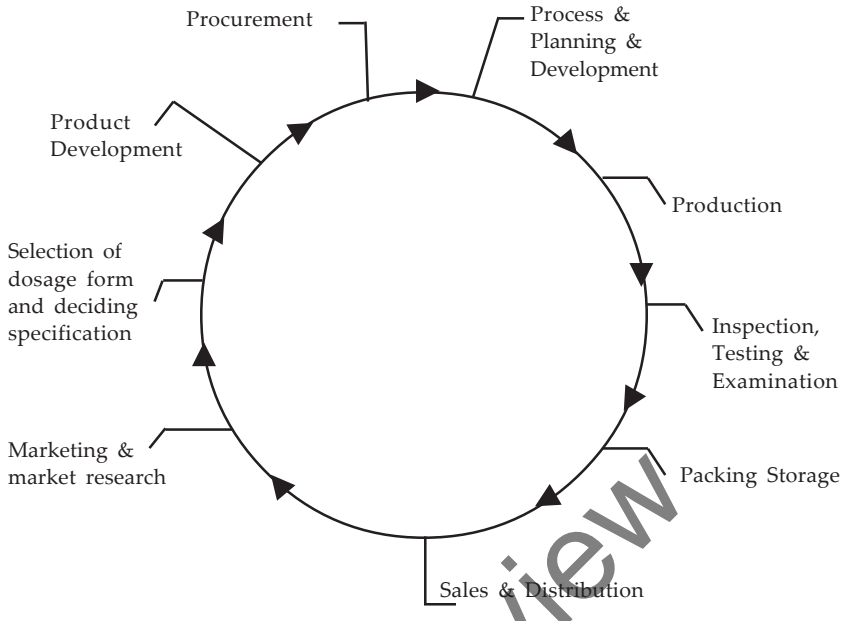


Fig. 1.2 – Quality Loop

carried out by several functional departments. The quality system applies to and interacts with all activities related to quality of a product or service. It can be explained through quality loop (Fig. 1.2). The quality system involves all phases from initial identification to final satisfaction of requirements and customer's expectation. ISO:9004(1994) states the following phases and activities for a quality system:

- Marketing & market research
- Design/specification engineering and product development
- Procurement
- Process planning and development
- Production
- Inspection, testing & examination
- Packaging & storage
- Sales & distribution
- Installation & operation
- Technical assistance & maintenance
- Disposal after use

The last three elements are not applicable to the items which are consumed after purchasing e.g. food items, drugs. The

last three elements apply to the items which are used for a longer time, for example, television, refrigerator etc.

In case of pharmaceutical formulations, element at S.No. 2 will be selection of dosage form deciding specifications and product development.

Relationship of these activities can also be explained through the spiral of progress in quality. Achievement of fitness for use involves a number of separate deeds & activities in a logical progression. The main activities in the progression have been shown in the spiral of progress (Fig. 1.3). A turn of the

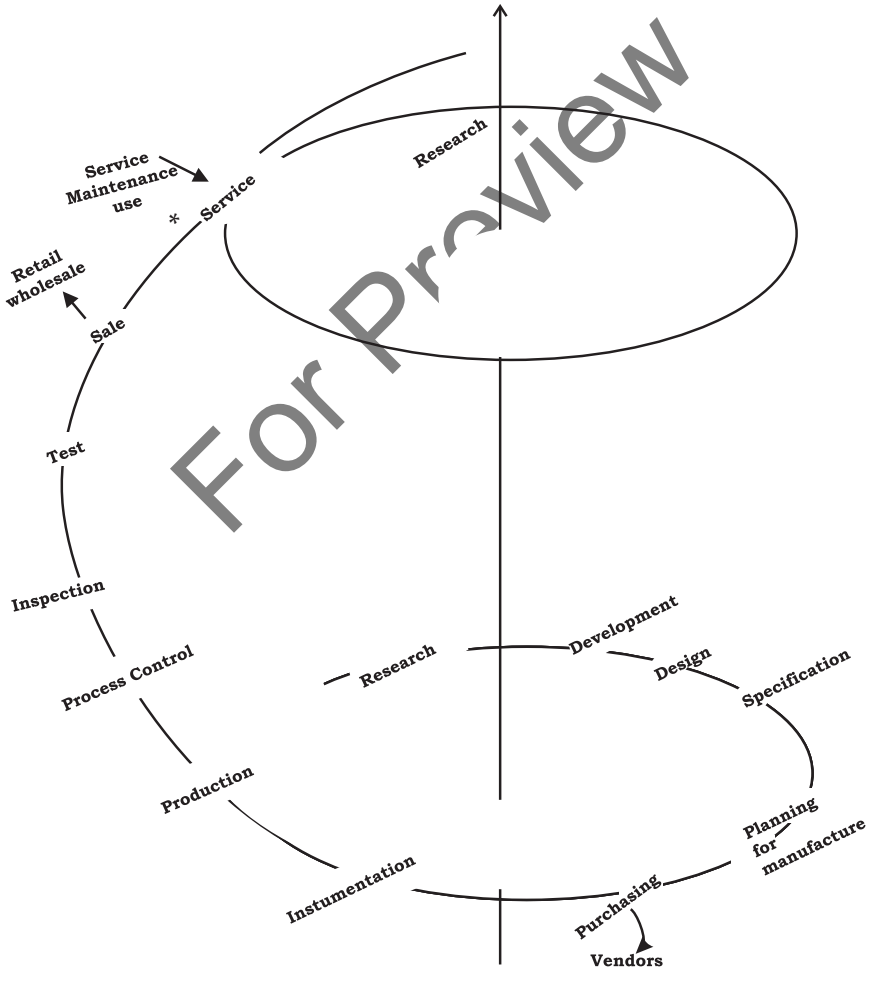


Fig. 1.3 – The Spiral of Progress in Quality

*Not relevant in case of pharmaceutical products

spiral of progress commences with product research & development to create an improvement in fitness for use, the object. At the end of that turn, the experience of user may create a new idea which will start a new turn of the spiral for improvement.

It may be seen from the spiral of progress in quality that activities needed to achieve the object, "fitness for use", are scattered among several persons in several specialized departments.

It may also be seen that some departments are in-house & some are not. The outside persons are a part of vendor companies, merchant companies, user companies, consumer families. In the companies, the specialized departments are also concerned with certain other functions, for example, cost, delivery, personnel, technology. From this, it can be very well made out that these departments have multiple goals as well. Today, this is a major problem how to make them conducive to each other or to harmonize them. These widely scattered activities constitute quality function.

Thus quality function can be defined as the entire collection of activities through which we achieve fitness for use, no matter where these activities are performed.

3. QUALITY CONTROL

The term, "quality control" comprises of two words quality & control. Control is universal regulatory process. In the industry, it takes the form of meeting standards. The process through which we establish & meet standards is called "control". This process has universal series of steps. Steps applied to the problem of quality can be listed as follows:

- choosing the control subject, means what is to be regulated or controlled;
- choosing an unit of measure;
- setting a standard value, means specifying quality characteristic (e.g. plus, minus limits);
- providing a device which can measure the characteristic in terms of the unit of the measure (e.g. pH meter, UV spectrophotometer);

- conducting actual measurements;
- interpreting the difference between actual & standard (e.g. pharmacopoeial or pre-determined value and the value actually found);
- taking decision and acting on the difference.

An extensive discussion on this universal series of steps appear in Managerial Breakthrough by Juran.[2]

When this universal regulatory process is applied to the problems of product quality, it is called *"quality control"*.

In context with pharmaceutical industry, quality control as defined in the text of WHO GMPs[3] may be considered adequate for clarity of the concept.

Quality Control (QC) includes activities like sampling, setting specifications, testing, organizing QC function, documentation, releasing product for sale etc.

All continuing performances are likely to have variations. Some of these variations are insignificant and are ignored and no corrective action is taken. But other variations are so significant that these trigger alarm signals. These variations are a form of sporadic departure from standard and demand that personnel responsible for control should act to restore status quo. For example, if tableting machine starts producing tablets which vary so much that the tablets do not pass weight variation test. This situation will require adjustment or other action depending on the cause.

Remedial action can be taken by discovering which process changes created the symptoms which triggered alarm signals. The sequence of events used to restore the status quo is known variously but most commonly as "trouble shooting".

In any system of control, the standard level of performance is regarded as goal also. In this concept, it is implied that it is not possible or it is not economical to improve the standard level of performance. But some determined men make improvements over standard level and make it obsolete, however, this process of making improvements differs from control process as at the very outset the standard level is itself regarded on the wrong level of performance. The difference between the old standard level & the new standard level is regarded as "chronic disease". When

a new superior level of performance is attained through determined efforts, it is called "break through".

When the quality control is achieved by utilizing all the strength of the company, it is considered as company-wide quality control (CWQC). The other terms which is used for this approach is total quality control (TQC).

4. QUALITY POLICY

All organizations have either in mind or in writing some principles, intentions, beliefs, creeds etc. which are their guides to managerial conduct. They rest on a philosophical and ethical base. They pertain to important issues and are intended to have long life. Such principles are known as policies.

In very small organization where one man makes all the decisions, these guides are in his mind. He operates in accordance with his unwritten code of conduct & his deeds reflect that code. This code (policy) is published by word-of-mouth. As organization grows, more than one man make decisions, the decisions taken by the managers affect people inside as well as outside the organization and the decisions may affect the managers also. If consistency is not there in the decisions, neither insiders nor outsiders can predict the expectations.

It is desirable to have predictability. An accepted way of creating predictability is to think, write down & publish the policies. These policies become the basis for consistent conduct.

It will be useful to write some thing about the subject matter. Quality policy statements are brief declarations like:

> '*It is the policy of M/s. ..... that its products will meet all specified & implied standards of quality*'.

However, such statements are regarded by the managers too vague to provide guidelines for the conduct. Nobody questions such statements. These policies are considered as motherhood policies. Choice of subject matter for quality policy may be varied. However, there are certain matters which are so fundamental that these should be considered by any company which is going to prepare written quality policy. These fundamental matters include the following:

- Which level of clientele constitute the organizations market? This matter will have bearing on the quality of design.
- Has the organization to strive for quality leadership or competitiveness or just adequacy?
- Has the organization been selling standard products or has it been selling a service in which the product is one of the ingredients of sale? This matter will have bearing on conformance to specifications.
- Has the organization to market its products on the basis of high reliability at higher initial price or lower reliability at lower initial price?
- Whether the effort is to be made to optimize user's cost or manufacturer's cost?
- Whether the abilities are to be quantified?
- Whether the organization is to rely for its controls on systems or on men?
- At which level quality planning is to be done?
- Whether the vendor is to be put on the team?
- Whether top management should participate in quality planning & assurance or these should be delegated to others?

Considerations mentioned above are general. Some considerations may not be applicable to drugs e.g. quantification of abilities.

When the organization grows to such an extent that it gets involved in multiple markets & products, no one set of quality policies can fit into its all activities, this problem can be solved by creating several levels of quality policy & one of the levels is corporate quality policy. A corporate quality policy consists of the statement of those policies which are company-wide in nature and are binding on all company's units. The corporate quality policy usually states the following:

- the purpose of writing & publishing quality policies;
- motherhood statement;
- the minimal actions to be taken by the divisions of the company with respect to quality;
- delegation of authority to divisions to establish subsidiary quality policies appropriate to their requirements as the divisions may be doing different types of activities;

– if required, quality policies for functional organization units or for programmed activities e.g. research and development.

While deciding & writing quality policy, following points may be considered:

– the policy should be relevant to the organization, its products and people;
– the objectives should be ambitious but achievable;
– the policy should be practical in approach & realistic;
– the policy should be written in easy to understand language.

In the process of formulating policies, the key managers should participate. However, they may not do detailed staff work. One way of doing this is to assign to a specialist the job of obtaining form these key managers the following:

– their nominations as to what should be the subject matter of quality policies;
– their judgment as to the direction of the company towards these subjects

Through this method, it is possible to find out consensus among these key managers on the identified subjects. A draft can be prepared based on the consensus which can be further discussed for finalizing the policies.

Until 1960s, examples of written quality policy were rare. Thereafter, the number is increasing & the increase is likely to continue. Under ISO certification process, it is necessary for a company to have written quality policy. Many companies in India are opting for ISO certification and therefore, number of written quality policy is increasing. While the written quality policy is mainly for internal use but broader publication may be necessary in view of the growing competition. Advantages of written policy are:

– it makes those concerned with it to think in depth as it can be written only after giving a thought;
– written policy can be communicated in authoritative uniform manner;
– it provides a basis for management by agreed policies rather than by crises or opportunities;
– audit of adherence to the policy can be done.

Before the policy is published, there should be firm determination to adhere to it. If there is any doubt in adherence to it, it should not be published. Because in long run, both insiders & outsiders draw their conclusions about the policy from the deeds of the company. If people see innovative products one after the other from a company they conclude that the company has policy of design leadership. If a company attends to quality complaints promptly, the observer will conclude that company has policy of ethical dealing on quality. If the deeds of the company are in line with the policy, the written policy gains credibility. If written policy says something and deeds tell something else, not only written policy of the company loses its credibility but other promises made by the company are looked at suspiciously. Therefore, it will be advisable to arrange audits to provide feedback on as to how well the policies are being followed.

5. QUALITY OBJECTIVES

The concept of management by objectives is widely practiced. Under this concept, managers participate in discussing objectives which are then reduced to writing and these become the basis for planning for results. These objectives are known as quality objectives. Well defined objectives help to unify thinking of managers, stimulate action and permit comparison of performance against objectives. Objectives may be either for breakthrough or for control. These terms have already been explained in preceding paragraphs.

In small organizations, the chief executive by personal observations and by direct contact with the people can set quality objectives. In large organization, this personal contact is no more feasible. If there is no other alternative, the leadership for setting quality objectives is passed on to the departmental heads & the quality objectives tend to be departmental rather than corporate. A large company can establish an interdepartmental mechanism to identify potential objectives, assess their economic & other effects & fix a priority in the program for action.

The inputs like given below can help in identifying quality objects:

- Pareto analysis of repeated external alarm signals (e.g. complaints, returns etc.)
- Pareto analysis of repeated internal alarm signals (e.g. rejection, reprocessing etc.);
- proposals from key persons in the organization i.e. managers, supervisors, professionals etc.;
- proposals from suggestion schemes;
- data from field study of user's needs, costs;
- comparison data on performance of the product versus competitor's product;
- comments of key people outside organization i.e. customers, vendors, critics, press etc.;
- findings or comments of regulatory agency, independent laboratories etc.

A small note on Pareto principle will be helpful here, Vilfredo Pareto, an Italian economist (1848-1923) had studied the distribution of wealth and had quantified the extent of inequality of this distribution. Although he had not generalized this concept of unequal distribution to other fields, but it was observed that the phenomenon of vital few & trivial many was universal. This phenomenon was later given the name of Pareto Principle.

An objective is not likely to get priority unless it is quantified as managers have multiple objectives for which they are accountable. In view of this, advocate of specific objectives should get them quantified so that these get priority. Some typical statements of quantification are as follows:

Nature of objective :	**Quantified goals**
Product Improvement :	To develop a headache tablet with reduced disintegration time of less than one minute within three months.
Training :	To conduct GLP training program for analysts within 30 days.
Cost reduction :	To reduce cost of packing material of product x by the first half of the financial year.

At the upper management level, quality objectives usually face competition form other objectives. Top management has

strong bias with respect to three vital criteria.

- Top management prefers objectives for breakthrough over the objectives for control. The former has potential for long range progress of the company while the latter is concerned with short-term targets. Further, in the latter case, top management tries to delegate responsibility to the lower levels.
- Top management exhibits a bias for projects of a business or management nature. Although technology is one of the means for meeting the business objectives, but-not many top managers understand it prospectively.
- In the company, there are two common languages. At the bottom of the company that is below supervisors, foreman etc. the language is in terms of "things". Any one at this level talks, he talks about units of products, man-hours or other materials or things. At the top of the company, common language is money that is investment, return on investment, sales, profits etc. It is through this common language top manager are able to make useful decisions. In such a situation, the middle managers & professionals should be bilingual. Only then they will be able to talk to the people at the bottom in the language of things and to the top management in the language of money. Common languages in the company have been shown in Fig. 1.4.

Middle management plays an important role in identifying and getting a quality objective approved from top management.

6. QUALITY ASSURANCE

Many a time, many people substitute the terms, "quality assurance" and "quality control" for each other. It should not be done. Quality assurance is a much wider term and quality control is a part of quality assurance. The terms, quality control and quality assurance have been defined variously by organizations like ISO, ANSI. According to one definition Quality Assurance (QA) is all planned and systematic activities implemented in a quality system to provide confidence that a product or service will fulfill requirements for quality.

In the WHO GMP text[4], QA has been stated to be a wide ranging concept covering all matters which either individually or collectively influence the quality of the product.

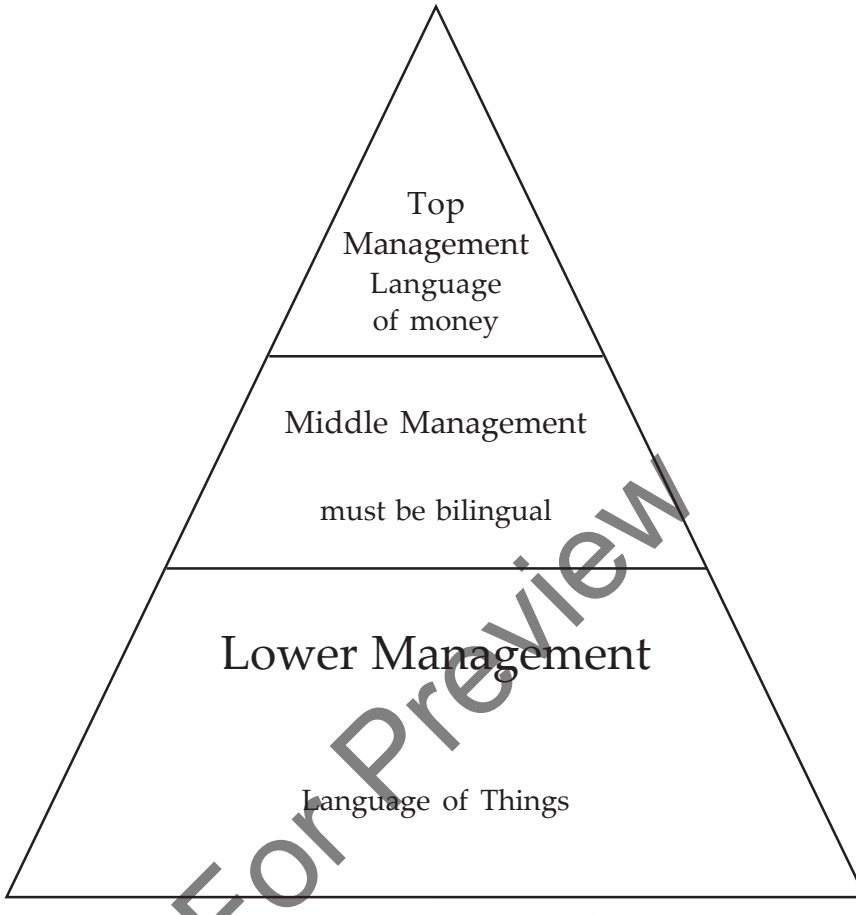


Fig. 1.4 – Common Languages in the Company

In general, before giving assurance to others one has to be sure himself. The assurance in quality is achieved through implementing various good practices like GMP, GLP, GPP.

The concept may be further simplified by stating that it is implementation of good clinical practices (GCP), good manufacturing practices (GMP), good laboratory practices (GLP), good pharmacy practices (GPP) and any other measures taken to achieve the intended objectives. In context with pharmaceutical industry, quality assurance can be represented as:

Quality assurance = GCP+GMP+GLP+GPP+other measures

In context with pharmaceutical manufacturing, reader may go through text of WHO GMP where QA is an element. In this

element, it has been stated that the quality system must ensure certain activities and that the manufacturer must assume the responsibility for the quality, efficacy and safety of the product.

The top managers are responsible for product's fitness for use and they are accountable to the directors, owners, regulators, public etc. These top managers can and often do delegate responsibility to subordinate managers for carrying out the activities that make up the quality function but they can not delegate the accountability.

7. QUALITY MANAGEMENT

Quality management is defined as that aspect of management function which determines and implements the quality policy i.e. overall intentions and direction of an organization regarding quality as formally declared & authorized by the top management. The responsibility & commitment to quality belongs to the highest level of management. The top management may adopt various management techniques and styles to achieve quality objectives.

The top management may consider the following action points to achieve quality objectives of the company:

- Quality policy should be defined & declared.
- Responsibility & authority of managers should be defined.
- A quality system should be established.
- Function of the quality system should be reviewed at regular intervals.
- Representatives of the management should be appointed at appropriate levels.
- An internal verification system should be established i.e. quality audit.

There are three prerequisites for implementation of quality management. These are quality policy, quality system and quality objectives.

The top management has several functions to look after. Therefore, it may not be possible for it to devote long time on quality management alone. Therefore, it becomes necessary to appoint a management representative to plan, implement, monitor

and control quality related activities. The management's representative should be delegated with appropriate authority & responsibility for taking decisions on behalf of the top management.

Responsibilities and authority of personnel who are involved in the management, performance & verification of quality related activities should be clearly defined by the top management. The individual person should have an understanding of his work, interrelationship, authority, and responsibility. He should have freedom to take action.

To find out whether the quality system is working effectively or not, a review of quality system should be taken periodically. If it is not functioning effectively, corrective measures should be taken.

The top management should establish an independent verification system. For this verification the top management should provide trained & qualified auditors & material resources. These auditors should submit a report to the management pointing out the deficiencies and suggestions for corrective measures. Readers may also see Section 3.3.2 of Chapter 9 for internal audit and management review.

8. ISO QUALITY SYSTEM CERTIFICATION

Readers must have come across statements like, ISO 9001 certified company. What is meant by such statements? To understand this, it is important to understand what is ISO, what is ISO 9000 series of standards & how are the organizations certified?

8.1 International Organization for Standardization (ISO)

ISO is a federation of national standards bodies. India is one of the founding members of ISO. At present, national standards institutes of 162 countries are the members.[5] India participates through Bureau of Indian Standards (BIS), a national standards body. The headquarters of the ISO is located at Geneva in Switzerland. The objective of ISO is to promote the development of standardization and associated activities with international trade of goods and services. The other objective of

ISO is to develop cooperation in the field of intellectual, scientific, technological and economic activity.

Like national standards bodies prepare national standards, ISO prepares international standards for goods and systems. Draft international standards adopted by technical committees are circulated to member bodies for approval before acceptance as international standards by ISO Council. At least 75% of the member bodies should approve the draft of international standards.

8.2 ISO 9000 Series of Standards (Quality Management Systems)

Originally ISO 9000 was a series of 5 international standards for quality management and quality assurance system. These standards are general in nature and, as such, can be adopted by any organization producing goods or providing services.

Bureau of Indian Standards (BIS) has adopted this series of standards as IS:14000 series of standards. ISO 9000 series standards and their equivalent Indian standards are given below:

ISO	IS	Title
ISO 9000 –1987	IS 14000 –1991	Quality systems – Guidelines for selection and use of standards on quality system
ISO 9001 –1987	IS 14001 –1991	Quality systems – Model for quality assurance in design/ development, production installation and servicing
ISO 9002 –1987	IS 14002 –1991	Quality systems – Model for quality assurance in production and installation
ISO 9003 –1987	IS 14003 –1991	Quality systems – Model for quality assurance in final inspection and test.
ISO 9004 –1987	IS 14004 –1991	Quality management and quality system elements – Guidelines.

The ISO 9000 series was first published in 1987 and was subsequently revised in 1994 and 2000. The 2000 version of ISO 9001: 2000 combines the three standards, 9001, 9002 and 9003 into one, now called as 9001.[6] Design & development procedures are required only when a company, in fact, is engaged in creation of new products. This version has radical change in thinking and has focus on process management rather than inspecting final product. The 2000 version also demands involvement of upper executives to integrate quality functions to junior executives. ISO 9001 : 2000 has been revised and currently 2008 version is the latest. This version is refinement of 2000 version. It introduces classification to the requirements.

The current versions of the remaining standards of 9000 series are:

ISO 9000 : 2005 – Quality management systems – Fundamentals and vocabulary

ISO 9004 : 2009 – Managing for sustained success of an organization – A quality management approach.

These standards can be downloaded from the website of ISO on payment.

The ISO 9000 standard provides the fundamentals and vocabulary used in the entire 9000 series of standards. It prepares the stage for understanding the basic elements of quality management as described in the ISO standards. It introduces the users to eight quality management principles and the use of the process approach to achieve continual improvement.

The ISO 9001 specifies the basic requirements for a quality management system (QMS) which an organization must fulfill to demonstrate its ability to provide products (which include services) consistently that enhance customer satisfaction and meet applicable statutory and regulatory requirements. This standard is used for certification. The certification is provided by certification bodies (CB). Consultants are available who help in procuring ISO 9001 certification. For the information of readers, contents of ISO 9001 : 2008 are given below:

Contents of ISO 9001 : 2008

1. Scope
   - 1.1 General
   - 1.2 Application
2. Normative references
3. Terms and definitions
4. Quality management system
   - 4.1 General requirements
   - 4.2 Documentation requirements
5. Management responsibility
   - 5.1 Management commitment
   - 5.2 Customer focus
   - 5.3 Quality policy
   - 5.4 Planning
   - 5.5 Responsibility, authority and communication
   - 5.6 Management review
6. Resource management
   - 6.1 Provision of resources
   - 6.2 Human resources
   - 6.3 Infrastructure
   - 6.4 Work environment
7. Product realization
   - 7.1 Planning of product realization
   - 7.2 Customer related processes
   - 7.3 Design and development
   - 7.4 Purchasing
   - 7.5 Production and service provision
   - 7.6 Control of monitoring and measuring equipment
8. Measurement, analysis and improvement
   - 8.1 General
   - 8.2 Monitoring and measurement
   - 8.3 Control of non-confirming product
   - 8.4 Analysis of data
   - 8.5 Improvement

Annex A
Annex B
Bibliography

ISO 9004 provides guidance on a wider range of objectives of quality management system than does ISO 9001, specially in managing the long term success of an organization. The ISO

recommend ISO 9004 as a guide for organization whose top management wishes to extend the benefits of ISO 9001 in pursuance of systematic and continual improvement of the organization's overall performance. But it is not intended for certification.

8.3 Certification

ISO itself does not certify companies or organizations. Several countries have formed accreditation bodies to authorize certification bodies which audit companies and organizations applying for ISO 9001 compliance certification. Both accreditation bodies as well as certification bodies charge fees for their services. Various accreditation bodies have mutual agreement with each other so that certificates issued by one of the Accreditation Certification Bodies (ACB) are accepted worldwide.

The applicant company or organization is assessed on the basis of extensive samples of its sites, functions, products and/or services and the processes. If there is non-compliance in certain areas they are communicated to management for rectification. If there are no major problems, Certification Bodies (CB) issue ISO 9001 certificate for the site visited after receiving action (improvement) plan from the management stating as to how any problems will be resolved.

An ISO certificate issued once is not for all the time. It has renewal date. It is required to be renewed at the intervals as recommended by CB. The validity of certificate usually is three years.

References

1. Reliability of Military Electronic Equipment, report by the Advisory Group on Reliability of Electronic Equipments, Office of the Asstt. Seretary Defence (R&D), June 1957.
2. Juran, J.M., Managerial Breakthrough, McGraw Hill Book Co., New York, 1964.
3. Quality Assurance of Pharmaceuticals, Vol. 2, WHO, Geneva, 2004, p. 52.
4. Quality Assurance of Pharmaceuticals, Vol. 2, WHO, Geneva, 2004, p. 16.
5. http://www.iso.org/iso/en/aboutiso/introduction/index.html
6. ISO: 9001-2008, International Organization for Standardization, Geneva.