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Good Manufacturing Practices (GMP) for Medicinal Products

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1. Introduction

The term GMP was introduced to regulate manufacturing and packaging operations in the pharmaceutical company. Until the mid-1960s, operating procedures for the manufacture of drugs consisted of formulae and the basic methods of making products. Written procedures were often concise and often relied on the individual operator's skill and experience. As batches of medicines increased in number and size, the operating procedures were inadequate to produce consistent and reliable products. Much attention had focused on the purity of medicinal substances. Pharmacopoeias and codices specified formulae for mixtures and other preparation, but gave little detailed information on the methods of preparation. The factors affecting processing and packaging procedures were becoming more apparent and the need for appropriate guidelines was evident (Lund, 1994).

The Medicines Inspectorate of the Department of Health and Social Security of England, in consultation with other interested bodies compiled the guide to GMP also known as the Orange Guide. The first edition of the guide was published in 1971, before any formal inspections of drug manufacturers had been carried out under the Medicines Act. It was a relatively light volume of 20 pages, and was reissued as a third impression in 1972, with the addition of a 2-page appendix on sterile medicinal products. Because of the color of its cover, it became known as the Orange Guide. The guide was therefore written at a time when the nature, extent, and special problems of the manufacturer of drugs were not completely known. A second, more substantial edition (52 pages, including five appendices) was published in 1977. A third edition (110 pages, five appendices) was published in 1983 (Lund, 1994). Subsequently, the 2002 edition of Rules and Guidance for Pharmaceutical Manufacturers and Distributors, commonly known as the 'Orange Guide', was published with many changes and additions to the detailed European Community guidelines on GMP. The Medicines and Healthcare products Regulatory Agency (MHRA) has published new edition of the Orange Guide in 2007.

In United States, the first GMP regulations were issued in 1963 and described the GMP to be followed in the manufacture, packaging, and storage of finished pharmaceutical products. GMP regulations were developed by the US FDA and issued the United States CFR Chapter 21 in 1978. The regulations were similar in concept to the Orange Guide, but were enforceable by law whereas the UK guide was advisory. US congress passed the Federal Anti-tampering Act in 1983, making it a crime to tamper with packaged consumer products.

In the 1980s, US FDA began publishing series of guidance documents that have had a major effect on our interpretation of current GMP (cGMP). A “Guide to Inspection of Computerized Systems in Drug Processing” was published in 1983 and “Guideline on General Principles of Process Validation” was published in 1987. In 1992 the congress passed the General Drug Enforcement Act. In March 1997, the US FDA issued 21 CFR Part 11 which dealt with the use of electronic records and signatures. In 2000, US FDA introduced a guidance document on the incorporation of risk management into device development (Nally, 2007).

In August 2002, the US FDA announced a new initiative, Pharmaceutical cGMPs for the 21st Century – A Risk Based Approach. The September 2004 final report summarized the significant changes in the development and implementation of a new operational framework based on quality system and risk management approaches (Nally, 1998). Also in September 2004, the publication of the Process Analytical Technology (PAT) initiative guidance document supported innovation and efficiency in pharmaceutical manufacturing with a risk management foundation (USFDA, 2004).

The first World Health Organization (WHO) draft on GMP was prepared at the request of the twentieth World Health Assembly (resolution WHA 20.34) in 1967 by a group of consultants. The revised text was discussed by the WHO Expert Committee on Specifications for Pharmaceutical Preparations in 1968 and published as an annex to its twenty-second report. The text was further reproduced in 1971 in the Supplement to the second edition of The International Pharmacopoeia (WHOTRS823, 1992).

Text on GMP was accepted as an integral part of WHO certification scheme on the quality of pharmaceutical products moving in international market by WHA in 1969. The WHA, in resolution No.WHA28.65 accepted the revised version of both the GMPs and the certification scheme in 1975. The revised text is published in Thirty-second Report of WHO Expert Committee on Specifications for Pharmaceutical Preparations: WHO TRS 823 in 1992 (Sharma, 1995). In 2003, WHO TRS 908 had revised the content of GMP in its Annex 4: Good Manufacturing Practices for pharmaceutical products: main principles (WHO TRS 908, 2003). Recently WHO TRS 961 has published the updated contents on GMP in Annex 3: WHO good manufacturing practices: main principles for pharmaceutical products (WHO TRS 961, 2011).

2. Importance of GMP

In the United States the Center for Drug Evaluation and Research (CDER) promotes and protects public health by assuring that safe and effective drugs are available to Americans. There exists different types of risk with medicines (Figure 1), one of which is a preventable adverse event, which can be caused by different reasons. One of the reasons for this event can be a product quality defect. This risk can be avoided by effective implementation of GMP (US FDA CDER, 2001).

Friedrich Nietzsche once said, “If you know the *why* for living, you can endure any *how*.” Everyone in our industry should know the story of how the GMP has come in practice. Most requirements were put in place as responses to tragic circumstances and to prevent future tragedies (Immel, 2005).

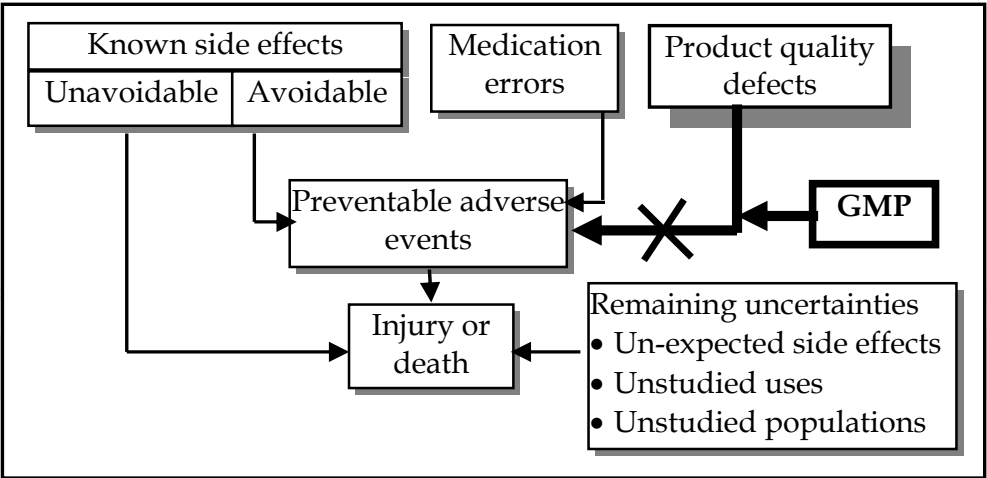


Fig. 1. Sources of Risk from Drug Products (Source: USFDA CDER 2001)

Sulfanilamide, a drug used to treat Streptococcal infections, had been shown to have dramatic curative effects and had been used safely for some time in tablet and powder form. In June 1937, however, a salesman for the S.E. Massengill Co., in Bristol, Tenn., reported a demand in the southern US states for the drug in liquid form. The company's chief chemist and pharmacist, Harold Cole Watkins, experimented and found that Sulfanilamide would dissolve in diethylene glycol. The company control laboratory tested the mixture for flavor, appearance, and fragrance and found it satisfactory. Immediately, the company compounded a quantity of Sulfanilamide elixir and sent shipments-all over the country (USA). The new formulation had not been tested for toxicity. At the time the food and drugs law did not require that safety studies be done on new drugs.

Because no pharmacological studies had been done on the new Sulfanilamide preparation, Watkins failed to note one characteristic of the solution. Diethylene glycol, a chemical normally used as antifreeze, is a deadly poison. The use of an oral Sulfanilamide elixir has caused the death of 107 people, many of them children before the problem was discovered. In response, US Congress passed the Federal Food, Drug and Cosmetic (FD&C) Act of 1938. For the first time, companies were required to prove that their products were safe before marketing them.

During 1960's Thalidomide was marketed in Europe as a sleeping pill and to treat morning sickness. When regulatory agencies gave permission to sell the drug for those indications, they knew nothing of its serious side effects. It turned out to be teratogenic: It caused serious deformities in developing fetuses. Children whose mothers took Thalidomide in the first trimester were born with severely deformed arms and legs. An estimated 10,000 cases of infant deformities in Europe were linked to Thalidomide use. Thalidomide galvanized public opinion. Two legislators, Kefauver and Harris, pushed more stringent legislation through US Congress that required companies to test not only to ensure that products were safe, but that they were efficacious for their intended uses (Immel, 2005).

Sharp, (1991) reported that at least 109 infants in Nigeria have died due to failure to follow GMP. This was caused due to the supply of mislabeled ethylene glycol as propylene glycol. This mislabeled material was then supplied to a pharmaceutical manufacturer. The manufacturer failed to perform adequate incoming quality control identification and

potency tests and final product evaluation did not pick up the problem. This has resulted due to failure in following GMP norms in manufacturing drugs. The effective implementation of GMP would prevent this mistake.

There was an incident of the outbreak of diethylene glycol poisoning that occurred in Haiti from November 1995 to June 1996 due to contamination of glycerol with diethylene glycol used in the preparation of paracetamol syrup. The incident led to some 89 deaths of children from Kidney failure. This was notified by the WHO through its newsletter no.10th Oct. 1996. The cause of fetal incident once again became the same deadly poisonous chemical diethylene glycol which casued the death of 107 people way back in 1937. The outbreak in Haiti emphasizes the need for pharmaceutical manufacturers' world wide to be aware of possible contamination of glycerol and other raw materials with diethylene glycol and to use appropriate quality control measure to identify and prevent potential contamination. This also has strengthened the enforcement of GMP guidelines to ensure safety and efficacy of the pharmaceutical products.

Effective implementation of GMP would also provide the cost benefit to the manufacturers, by avoiding the cost of failures such as cost of waste, of rework, of recall, of consumer compensation, of company reputation, and of regulatory action suspending operations.

3. Good Manufacturing Practices (GMP) guidelines

GMP is a production and testing practice that helps to ensure a quality product. Many countries have legislated that pharmaceutical and medical device companies must follow GMP procedures, and have created their own GMP guidelines that correspond with their legislation. Basic concepts of all of these guidelines remain more or less similar to the ultimate goals of safeguarding the health of the patient as well as producing good quality medicine, medical devices or active pharmaceutical products

GMP guidelines are not prescriptive instructions on how to manufacture products. They are a series of general principles that must be observed during manufacturing. When a company is setting up its quality program and manufacturing process, there may be many ways it can fulfill GMP requirements. It is the company's responsibility to determine the most effective and efficient quality process. The formalization of GMP commenced in the 1960s and they are now in effect in over 100 countries ranging from Afghanistan to Zimbabwe. Although many countries have developed local requirements, many also rely on the World Health Organization recommended GMP (WHO GMP) for pharmaceutical products. Regional requirements have also appeared with application to several countries. Examples of these include the following.

- a. Pharmaceutical Inspection Convention (PIC)—guide to GMP for pharmaceutical products—Australia, Austria, Belgium, Canada, Denmark, Finland, France, Hungary, Ireland, Italy, Latvia, Liechtenstein, Malaysia, The Netherlands, Norway, Poland, Portugal, Romania, Singapore, Slovak Republic, Spain, Sweden, Switzerland, and the United Kingdom.
- b. Association of South-East Asia Nations (ASEAN)—GMP: general guidelines—Brunei Darussalaam, Cambodia, Indonesia, Lao PDR, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam.

- c. European Economic Community (EEC)—guide to GMP for medicinal products—Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, Sweden, and the United Kingdom.

The above mentioned guidelines are similar in design and content and model more of a quality management approach or principle when compared with product testing and control more prevalent in the U.S. cGMP. Over the years, these regulations/guides have also been supplemented by descriptive guidelines providing additional information on specific topics. In general, GMP have been issued as guides to the achievement of consistent product quality, with interpretation and individual variations being accepted. GMP are enforced in the United States by the US FDA, under Section 501(B) of the 1938 Food, Drug, and Cosmetic Act (21 USCS § 351). The regulations use the phrase "current good manufacturing practices" (cGMP) to describe these guidelines.

The World Health Organization (WHO) version of GMP is used by pharmaceutical regulators and the pharmaceutical industry in over one hundred countries worldwide, primarily in the developing world including country like Nepal. The European Union's GMP (EU-GMP) enforces similar requirements to WHO GMP, as does the Food and Drug Administration's version in the US. Similar GMPs are used in other countries, with Australia, Canada, Japan, Singapore and others having highly developed/sophisticated GMP requirements. In the United Kingdom, the Medicines Act (1968) covers most aspects of GMP in what is commonly referred to as "The Orange Guide", which is officially known as Rules and Guidance for Pharmaceutical Manufacturers and Distributors.

In general, GMP inspections are performed by national regulatory agencies. GMP inspections are performed in the United Kingdom by the Medicines and Healthcare Products Regulatory Agency (MHRA); in the Republic of Korea (South Korea) by the Korea Food & Drug Administration (KFDA); in Australia by the Therapeutic Goods Administration (TGA); in South Africa by the Medicines Control Council (MCC); in Brazil by the Agência Nacional de Vigilância Sanitária (National Health Surveillance Agency Brazil) (ANVISA). In India GMP inspections are carried out by state Food and Drug Administration (FDA) and these FDA report to Central Drugs Standard Control Organization: in Nepal, GMP inspections are carried out by the Department of Drug Administration (DDA), and in Pakistan by the Ministry of Health. Nigeria has National Agency for Food and Drug Administration and Control (NAFDAC). Each of the inspectorates carry out routine GMP inspections to ensure that drug products are produced safely and correctly; additionally, many countries perform pre-approval inspections (PAI) for GMP compliance prior to the approval of a new drug for marketing (Wikipedia, 2012a).

4. Components of GMP

GMP requires that the manufacturing process is fully defined before being initiated and all the necessary facilities are provided. In practice, personnel must be adequately trained, suitable premises and equipment used, correct materials used, approved procedures adopted, suitable storage and transport facilities available, and appropriate records made. The essential components of GMP are summarized in Figure 2 (Lund, 1994).

The manufacturing premises of good design and regularly monitored is the most important component. There should be quality control of finished product, raw materials and

packaging materials. The equipment of good design is to be considered and all the equipments are required to be maintained properly. There should be a correct choice of cleaning equipment. The staffs should be trained well and should be wearing protective clothing while on work. There should be written procedures for carrying out the operations.

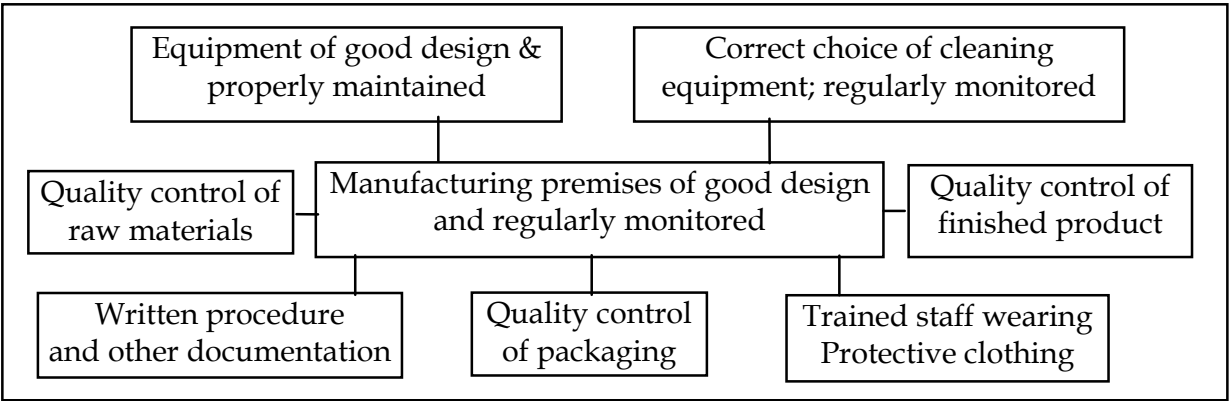


Fig. 2. Components of Good Manufacturing Practice (Source: Lund, 1994)

WHO Expert Committee on Specifications for Pharmaceutical Preparations had published the Forty-fifth Report of WHO TRS 961 in 2011. The committee reviewed the revision of the GMP text in the light of comments received from interested parties and brought out the basic guidelines on GMP in an Annex 3 under the title “WHO good manufacturing practice: main principles for pharmaceutical products.”

Among other feedback which was discussed during the consultation on WHO guidelines for medicines quality assurance, quality control laboratories and transfer of technology on 27–31 July 2009, the need was identified to incorporate a new section on “Product quality review” under Chapter 1: “Quality assurance”. In addition, several updates were suggested to further enhance the guidelines and include the concept of risk management, replacing “drugs” by the term “medicines” and newly introduce the concept of a “quality unit”. Quality unit is an organizational unit independent of production which fulfils both quality assurance (QA) and quality control (QC) responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

This has highlighted the different requirements of GMP as “Quality management in the medicines industry: philosophy and essential elements”. The essential elements described in detail includes; Quality assurance, Good manufacturing practices for pharmaceutical products, Sanitation and hygiene, Qualification and validation, Complaints, Product recalls, Contract production and analysis, Self-inspection, quality audits and supplier’s audits and approval, Personnel, Training, Personal hygiene, Premises, Equipment, Materials, Documentation, Good practices in production and Good practices in quality control (WHOTRS 961, 2011).

Volume 4 of "The rules governing medicinal products in the European Union" contains guidance for the interpretation of the principles and guidelines of good manufacturing practices for medicinal products for human and veterinary use. Its 1998 edition contains nine chapters describing Quality management, Personnel, Premises and Equipment,

Documentation, Production, Quality control, Contract manufacturing and analysis, Complaints and Product recall and Self Inspection as basic requirements of GMP with 14 annexes. Currently the guide is presented in three parts and supplemented with a series of annexes. Part I covers basic requirements for medicinal products, Part II covers basic requirements for active substances used as starting materials and Part III contains GMP related documents, which clarify the regulatory expectations (EudraLex, 2012).

Pharmaceutical inspection convention/Pharmaceutical Inspection Co-operation Scheme (PIC/S) had published PE 009-2 Guide to GMP for medicinal products in 2004. In order to further facilitate the removal of barriers to trade in medicinal products, to promote uniformity in licensing decisions and to ensure the maintaining of high standards of quality assurance in the development, manufacture and control of medicinal products throughout Europe, it was agreed to harmonize the rules of GMP applied under Pharmaceutical Inspection Convention (PIC) and the Pharmaceutical Inspection Co-operation Scheme (PIC/S) to those of the EU Guide to Good Manufacturing Practice for Medicinal Products and its Annexes. The guide contains nine chapters describing Quality management, Personnel, Premises and Equipment, Documentation, Production, Quality control, Contract manufacturing and analysis, Complaints and Product recall and Self Inspection with 18 annexes.

US FDA ensures the quality of drug products by carefully monitoring drug manufacturers' compliance with its cGMP regulations. Section 21 of the CFR contains most regulations pertaining to food and drugs. The regulations document the actions of drug sponsors that are required under Federal law. 21 CFR Part 210. cGMP in manufacturing processing, packing, or holding of drugs. 21 CFR Part 211. cGMP for finished pharmaceuticals. The CFR 21 part 211 dealing with cGMP for finished pharmaceuticals consists of Subparts A to K describing different components as General Provisions, Organization and Personnel, Building and Facilities, Equipment, Control of Components and Drug Product Containers and Closures, Production and Process Controls, Packaging and Labeling Control, Holding and Distribution, Laboratory Controls, Records and Reports and Returned and Salvaged Drug Products (Revised as of April 1, 2011).

The ASEAN GMP general guidelines have covered following elements such as Personnel, Premises, Sanitation, Equipment, Starting Materials, Production, Quality Control, Self Inspection, Handling of product complaint, product recall and returned drug products and Documentation, (ASEAN, 2000).

Indian schedule M for GMP and requirements of premises, plant and equipment for pharmaceutical products consists of Part I mentioning GMP for Premises and Materials. The Part I includes General requirements, Warehousing area, Production area, Ancillary area, Quality control area, Personnel, Health, clothing and sanitation of workers, Manufacturing operations and controls, Sanitation in the manufacturing premises, Raw materials, Equipment, Documentation and Records, Labels and other printed materials, Quality assurance, Self inspection and quality audit, Quality control system, Specification, Master formula records, Packing records, Batch packaging records, Batch processing records, Standard operating procedures (SOPs) and records, Reference samples, Reprocessing and recoveries, Distribution records, Validation and process validation, Product recalls, Complaints and adverse reactions and Site-master file. Part I-A to part I-E mentions about

the specific requirements for manufacture of different products and Part I-F mentions about the specific requirements of premises, plant and materials for manufacture of active pharmaceutical ingredients (bulk drugs). Part II describes the Requirement of plant and equipments for various dosage forms (Schedule M).

Worldwide, there are now around 30 different official national and super national statements on GMP. These have been published variously as guides, codes and regulations and of the 30 or so of them, two stand out as being the most influential and most frequently referenced: The United States Current Good Manufacturing Practice (cGMP) Regulations and the European Commission’s “Good Manufacturing Practices for Medicinal Products for Human and Veterinary Use”. Thirdly the WHO version of GMP is used by the pharmaceutical regulators and the pharmaceutical industry in over 100 countries worldwide, primarily in the developing world (Nally, 2007).

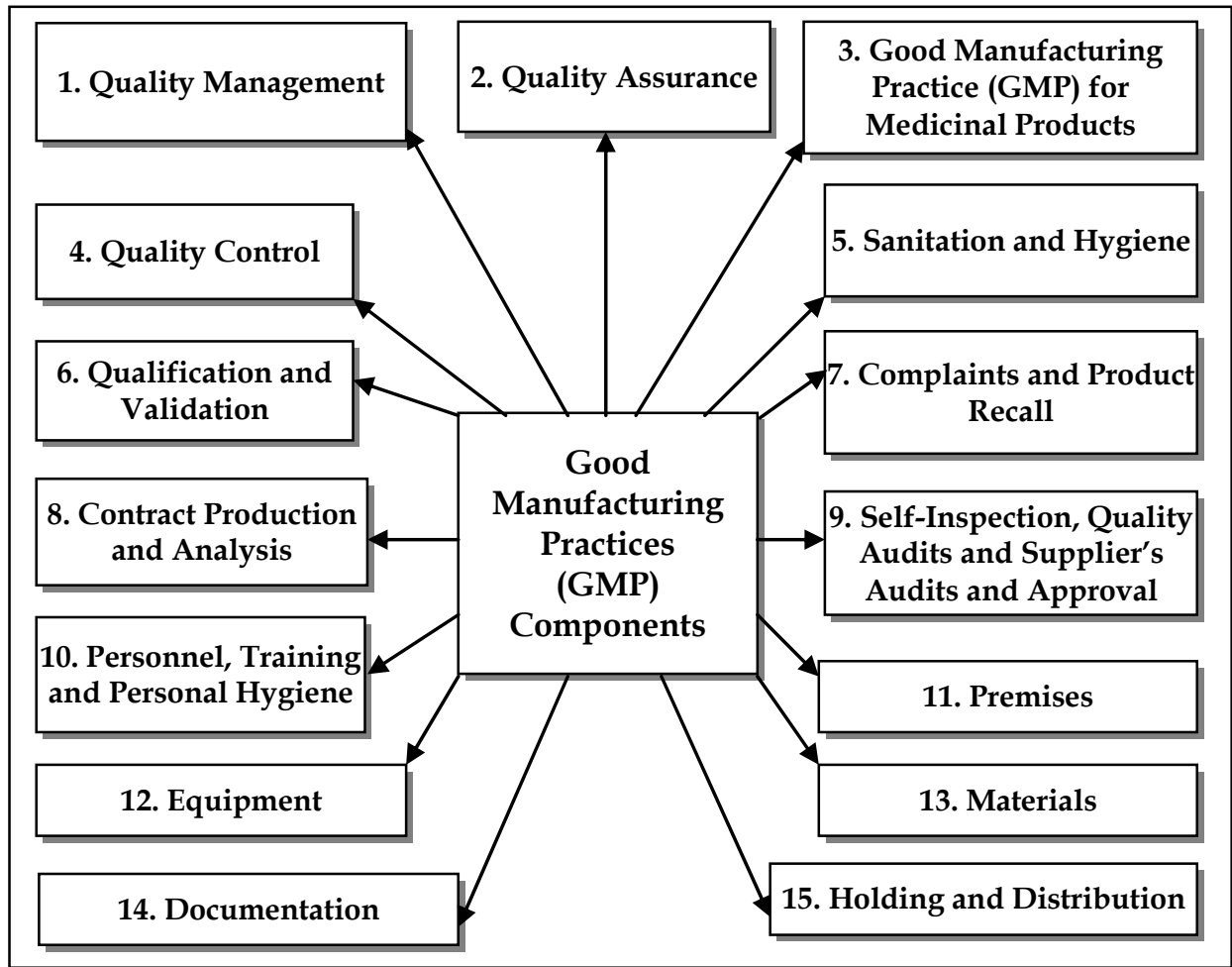


Fig. 3. Consolidated Components of Good Manufacturing Practices

While reviewing all the above documents, it is realized that most of the components identified for GMP aspects are similar in all the guidelines and publications. Based on the above discussion, the following components of GMP would cover all the requirements made by different authorities and also satisfy the WHO GMP guidelines for drug manufacturing: Quality management, Quality assurance, Good manufacturing practices for medicinal

products, Quality control, Sanitation and hygiene, Qualification and validation, Complaints and product recalls, Contract production and analysis, Self-inspection, quality audits and supplier's audits and approval, Personnel training and personal hygiene, Premises, Equipment, Materials, Documentation and Holding and Distribution. These consolidated components shown in Figure 3 are dealt one by one independently with reference to above mentioned GMP statements.

4.1 Quality management

The holder of a Manufacturing Authorization must manufacture medicinal products so as to ensure that they are fit for their intended use, comply with the requirements of the Marketing Authorization and do not place patients at risk due to inadequate safety, quality or efficacy. The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment by staff in many different departments and at all levels within the company, by the company's suppliers and by the distributors (EudraLex, 2012). In the pharmaceutical industry at large, quality management is usually defined as the aspect of management function that determines and implements the "quality policy", i.e. the overall intention and direction of an organization regarding quality, as formally expressed and authorized by top management (WHOTRS 961, 2011).

The basic elements of quality management are: an appropriate infrastructure or "quality system", encompassing the organizational structure, procedures, processes and resources; and systematic actions necessary to ensure adequate confidence that a product (or service) will satisfy given requirements for quality.

4.2 Quality Assurance (QA)

QA is a wide-ranging concept, which covers all matters, which individually or collectively influence the quality of a product. It is the sum total of the organized arrangements made with the objective of ensuring that pharmaceutical products are of the quality required for their intended use. QA, therefore, incorporates GMP and other factors such as product design and development.

The system of QA appropriate for the manufacture of pharmaceutical products should ensure that: (a) pharmaceutical products are designed and developed in a way that takes account of the requirements of GMP and other associated codes such as those of good laboratory practice (GLP) and good clinical practice (GCP); (b) production and control operations are clearly specified in a written form and GMP requirements are adopted; (c) managerial responsibilities are clearly specified in job descriptions; (d) arrangements are made for the manufacture, supply and use of the correct starting and packaging materials; (e) all necessary controls on starting materials, intermediate products, and bulk products and other in-process controls, calibrations, and validations are carried out; (f) the finished product is correctly processed and checked, according to the defined procedures; (g) pharmaceutical products are not sold or supplied before the authorized persons have certified that each production batch has been produced and controlled in accordance with the requirements of the marketing authorization and any other regulations relevant to the production, control and release of pharmaceutical products; (h) satisfactory arrangements exist to ensure, as far as possible, that the pharmaceutical products are stored by the

manufacturer, distributed, and subsequently handled so that quality is maintained throughout their shelf-life; (i) here is a procedure for self-inspection and/or quality audit that regularly appraises the effectiveness and applicability of the QA system; (j) deviations are reported, investigated and recorded; (k) there is a system for approving changes that may have an impact on product quality; (l) regular evaluations of the quality of pharmaceutical products should be conducted with the objective of verifying the consistency of the process and ensuring its continuous improvement; and (m) there is a system for quality risk management (QRM).

4.2.1 Product quality review

Regular periodic or rolling quality reviews of all licensed medicinal products, including export-only products, should be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product to highlight any trends and to identify product and process improvements. Such reviews should normally be conducted and documented annually, taking into account previous reviews, and should include at least: (i) a review of starting materials including packaging materials used for the product, especially those from new sources; (ii) a review of critical in-process controls and finished product results; (iii) a review of all batches that failed to meet established specification(s) and their investigation; (iv) a review of all significant deviations or non-conformances, the related investigations, and the effectiveness of resultant corrective and preventative actions taken; (v) a review of all changes made to the processes or analytical methods; (vi) a review of dossier variations submitted, granted or refused; (vii) a review of the results of the stability monitoring programme and any adverse trends; (viii) a review of all quality-related returns, complaints and recalls and the investigations performed at the time; (ix) a review of adequacy of any other previous corrective actions on product process or equipment; (x) for new dossiers and variations to the dossiers, a review of post-marketing commitments; (xi) the qualification status of relevant equipment and utilities, e.g. heating, ventilation and air-conditioning (HVAC), water, or compressed gases; and (xii) a review of technical agreements to ensure that they are up to date (WHOTRS 961, 2011).

4.2.2 Quality Risk Management (QRM)

QRM is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively. The quality risk management system should ensure that:

- the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient; and
- the level of effort, formality and documentation of the QRM process is commensurate with the level of risk.

4.3 Good Manufacturing Practice (GMP) for medicinal products

GMP is that part of QA which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorizations or product specification. GMP is aimed primarily at diminishing

the risks inherent in any pharmaceutical production. Such risks are essentially of two types: cross-contamination (in particular of unexpected contaminants) and mix ups (confusion) caused by, for example, false labels being put on containers.

The basic requirements of GMP are that: (a) all manufacturing processes are clearly defined, systematically reviewed in the light of experience, and shown to be capable of consistently manufacturing pharmaceutical products of the required quality that comply with their specifications; (b) qualification and validation are performed; (c) all necessary resources are provided; (d) instructions and procedures are written in clear and unambiguous language, specifically applicable to the facilities provided; (e) operators are trained to carry out procedures correctly; (f) records are made during manufacture to show that all the steps required by the defined procedures and instructions have in fact been taken and that the quantity and quality of the product are as expected; any significant deviations are fully recorded and investigated; (g) records covering manufacture and distribution, which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form; (h) the proper storage and distribution of the products minimizes any risk to their quality; (i) a system is available to recall any batch of product from sale or supply; and (j) complaints about marketed products are examined, the causes of quality defects investigated, and appropriate measures taken in respect of the defective products to prevent recurrence (WHOTRS 961, 2011).

4.4 Quality Control (QC)

QC is that part of GMP which is concerned with sampling, specifications and testing, and with the organization, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory. QC is not confined to laboratory operations, but may be involved in many decisions concerning the quality of the product. QC as a whole will also have other duties, such as to establish, validate and implement all QC procedures, to evaluate, maintain, and store the reference standards for substances, to ensure the correct labeling of containers of materials and products, to ensure that the stability of the active pharmaceutical ingredients (APIs) and products is monitored, to participate in the investigation of complaints related to the quality of the product, and to participate in environmental monitoring. All these operations should be carried out in accordance with written procedures and, where necessary, recorded (WHOTRS 961, 2011).

4.5 Sanitation and hygiene

A high level of sanitation and hygiene should be practiced in every aspect of the manufacture of medicine products. The scope of sanitation and hygiene covers personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection, and anything that could become a source of contamination to the product. Potential sources of contamination should be eliminated through an integrated comprehensive programme of sanitation and hygiene. Premises used in the manufacture, processing, packing, or holding of a drug product shall be maintained in a clean and sanitary condition. Any such building shall be free of infestation by rodents, birds, insects, and other vermin (other than laboratory animals). There shall be written procedures

assigning responsibility for sanitation and describing in sufficient detail the cleaning schedules, methods, equipment, and materials to be used in cleaning the buildings and facilities; such written procedures shall be followed. Records should be maintained.

Substance	Suitable Concentration	Effect on Bacteria	Effect on Spores	Effect on Vegetative Fungi	Advantages	Disadvantages
Ethanol	70%	Good	Fair	Fair	Quick acting; evaporates rapidly, leaving no residues	Limited range of effect; no flammable
Phenols	0.5-3%	Excellent	Good	Excellent	Broad range of effect; may be combined with surfactants	Corrosive on some surfaces (including skin)
Formaldehyde		Excellent	Good	Good	Broad range of effect; used for “gassing”	Premises not accessible during treatment; can be corrosive; short- and long-term human toxicity problems
Isopropanol	70-90%	Good	Good	Good	Quick acting; evaporates, leaving no residues	Not the most effective
Iodine and iodophors	75-150 ppm	Excellent	Good	Excellent	Quick acting; effective in low concentration	Can be corrosive; stains some surfaces
Chlorine compounds (hypochlorite, chloramines, etc.)	1-4%	Excellent	Good	Excellent	Broad range of effect	Corrosive
Quaternary ammonium compounds	1-5%	Good	Fair	Fair	Some cleaning effect; odorless	Limited effect; inactivated by soap detergents

Table 1. Disinfectants for Premises – Types and Applications (Source: Sharp, 2005)

The areas, surfaces, and equipment in and on which products are made must be kept clean. Dirt, and the microbes that it can harbor, must not get into or on products. Disinfectants can be inactivated by dirt. Dirt (particularly oily or greasy films and protein like matter) can also protect microorganisms against the action of disinfectants. So, before disinfection, it is important to first clean surfaces. Where gross amounts of dirt are present, it may be necessary to first remove most of it by scrubbing. Then surfaces may be cleaned by the application of a cleaning agent, followed by rinsing.

A wide range of substances are used as disinfectants. They may be single substances, like alcohols or phenols, and there are a number of commercially available mixtures. It is usually best not to make “do it yourself” mixtures. It could be dangerous, and some disinfectants

can neutralize each other's activity. Disinfecting agents vary in the range of their activity and in the concentrations at which they are effective. All have their own special advantages and disadvantages. Some examples of disinfectants, with their range of effects, etc. are shown in Table 1. Disinfectants should always be used in accordance with instructions and at the right dilution (instructions as given either in the supplier's literature or in company procedures). Since some microorganisms can grow readily in dilute disinfectants, dilutions of disinfectants should not be stored unless they are sterilized. Otherwise, dilutions should be made freshly each time they are needed. It is advisable to use different disinfectants over a period of time, on an alternating, or rotating, basis to prevent the development of disinfectant-resistant strains of microorganisms.

4.5.1 Personal hygiene

All personnel, prior to and during employment, as appropriate, should undergo health examinations. Personnel conducting visual inspections should also undergo periodic eye examinations. All personnel should be trained in the practices of personal hygiene. Any person shown at any time to have an apparent illness or open lesions that may adversely affect the quality of products should not be allowed to handle starting materials, packaging materials, in-process materials or medicines products until the condition is no longer judged to be a risk. Direct contact should be avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product. To ensure protection of the product from contamination, personnel should wear clean body coverings appropriate to the duties they perform, including appropriate hair covering. To reduce the risk of infection through hand contact, the following should be instructed to all operators:

- Do not touch the product/objects that may come in contact with the product, with unprotected hands.
- Keep the hands well groomed with short, clean nails. Hands must be free of any lesions, wounds, cuts, boils, or any other sources of infection.
- Wrist watches, rings, or other jewelry should not be worn on the job.
- Hands should be washed before work and as often as the job requires (Figure 4).
- Protective gloves should be worn when working with open products and when handling objects that come in direct contact with the product.

Smoking, eating, drinking, chewing, and keeping plants, food, drink, smoking material and personal medicines should not be permitted in production, laboratory and storage areas. Personal hygiene procedures including the use of protective clothing should apply to all persons entering production areas, whether they are temporary or full-time employees or nonemployees, e.g. contractors' employees, visitors, senior managers and inspectors.

4.6 Qualification and validation

Qualification is an action of proving that any premises, systems and items of equipment work correctly and actually lead to the expected results. Validation is defined as the establishing of documented evidence which provides a high degree of assurance that a planned process will consistently perform according to the intended specified outcomes. Validation studies should reinforce GMP and be conducted in accordance with defined procedures. Results and conclusions should be recorded. When any new manufacturing formula or method of preparation is adopted, steps should be taken to demonstrate its

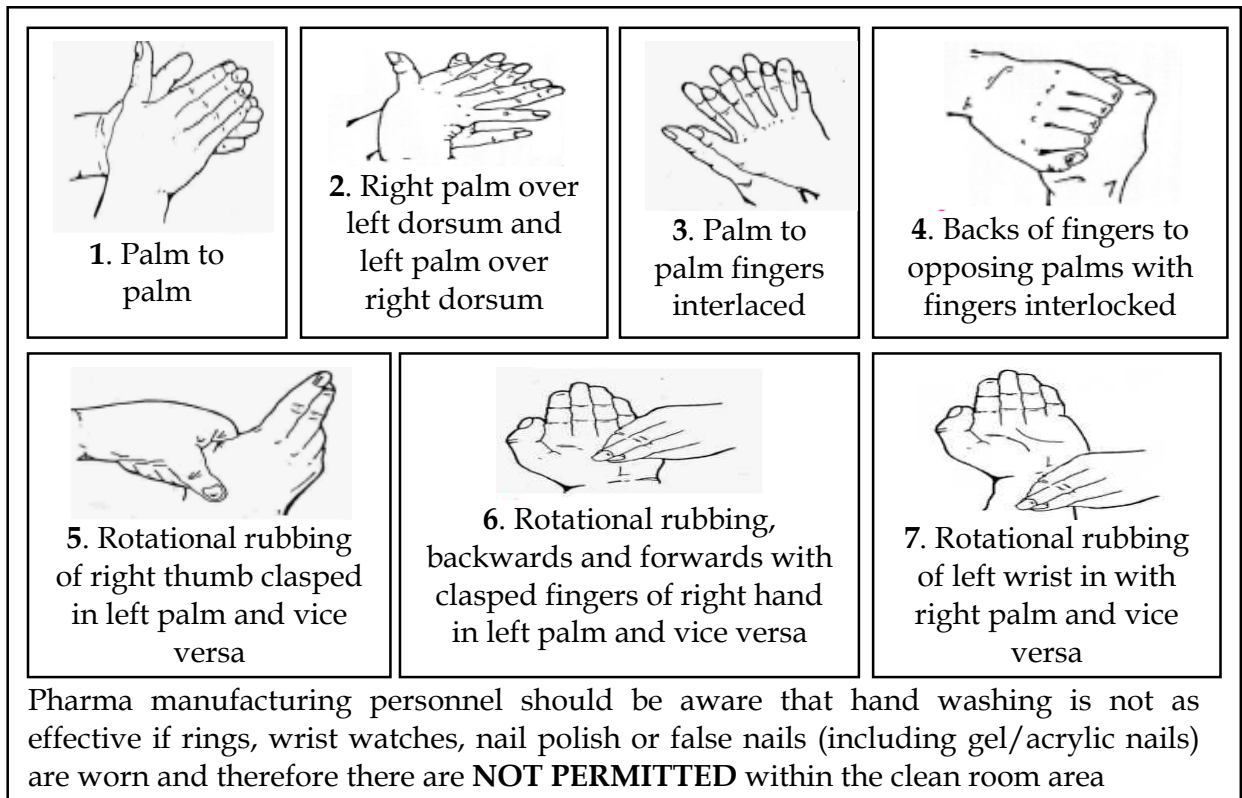


Fig. 4. Seven Steps to Effective Hand Washing

suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to yield a product consistently of the required quality. Significant amendments to the manufacturing process, including any change in equipment or materials, which may affect product quality and/or the reproducibility of the process, should be validated. Processes and procedures should undergo periodic critical revalidation to ensure that they remain capable of achieving the intended results (PIC/S, 2004). Every step of the process of manufacture of a medicinal product must be shown to perform as intended. Once the system or process has been validated, it is expected that it remains in control, provided no changes are made. In the event that modifications are made, or problems occur, or equipment is replaced or relocated, revalidation is performed. The validity of systems/equipment/tests/processes can be established by prospective, concurrent or retrospective studies.

Qualification and validation should establish and provide documentary evidence that: (a) the premises, supporting utilities, equipment and processes have been designed in accordance with the requirements for GMP (design qualification or DQ); (b) the premises, supporting utilities and equipment have been built and installed in compliance with their design specifications (installation qualification or IQ); (c) the premises, supporting utilities and equipment operate in accordance with their design specifications (operational qualification or OQ); and (d) a specific process will consistently produce a product meeting its predetermined specifications and quality attributes (process validation or PV, also called performance qualification or PQ).

4.6.1 Validation protocols and validation master plan

A protocol is a written set of instructions broader in scope than a Standard Operating Procedure (SOP). A protocol describes the details of a comprehensive planned study to investigate the consistent operation of new system/equipment, a new procedure, or the acceptability of a new process before it is implemented. The Validation Master Plan (VMP) is a high-level document which establishes an umbrella validation plan for the entire project, and is used as guidance by the project team for resource and technical planning (also referred to as master qualification plan). VMP describes which equipment, systems, methods and processes will be validated and when they will be validated. The document should provide the format required for each particular validation document (Installation Qualification, Operational Qualification and Performance Qualification for equipment and systems; Process Validation; Analytical Assay Validation), and indicate what information is to be contained within each document.

4.6.2 Analytical procedures and methods validation

Method validation is the process used to confirm that the analytical procedure employed for a specific test is suitable for its intended use. Results from method validation can be used to judge the quality, reliability and consistency of analytical results; it is an integral part of any good analytical practice. Analytical methods need to be validated or revalidated before their introduction into routine use; whenever the conditions change for which the method has been validated (e.g., an instrument with different characteristics or samples with a different matrix); and whenever the method is changed and the change is outside the original scope of the method (Huber, 2012).

The parameters for method validation have been defined in different working groups of national and international committees and are described in the literature. Unfortunately, some of the definitions vary between the different organizations. An attempt at harmonization was made for pharmaceutical applications through the ICH, where representatives from the industry and regulatory agencies from the United States, Europe and Japan defined parameters, requirements and, to some extent, methodology for analytical methods validation. The parameters, as defined by the ICH and by other organizations and authors, are summarized in Table 2.

Selectivity and Specificity (1,2) and	Precision (1,2) and reproducibility (3)
Accuracy (1,2) and Recovery	Linearity (1,2)
Range (1,2)	Limit of detection (1,2)
Limit of quantitation (1,2)	Robustness (2,3)
Ruggedness (2)	
(1) Included in ICH, (2) Included in USP, (3) Terminology included in ICH publication but not part of required parameters	

Table 2. Possible Analytical Parameters for Method Validation (Source: Huber, 2012)

4.7 Complaints and product recalls

QA and GMP are about preventing errors. However, in this imperfect universe there is no such thing as an infallibly perfect system, and an essential feature of any QA system is a

plan for dealing with complaints, or reports of faulty products, if they do occur. A requirement to cover this occurs in all notable GMP guidelines. Complaints received from consumers, professionals, and the trade serves as a primary means of obtaining feedback about product quality after distribution. It is necessary, therefore, that each complaint or inquiry be evaluated by knowledgeable and responsible personnel (Nally, 2007).

The records of production, packaging, and distribution of drug and the retained samples provide the basis for assessing the validity and seriousness of the alleged deviations that precipitated the complaint. The complaint file itself also plays an important role in determining whether any other similar complaints have been received on the lot in question, or on any other lots of the same product. The evaluation of complaints serves several valuable purposes. First, there is the urgent need to confirm whether consumers are potentially at risk and to initiate any appropriate action. A second value is the review of the product and its production process to establish whether any modifications are required. Third is the need to rapidly respond to the customer, thereby attempting to maintain confidence in the product and company.

Manufacturers should have a written recall procedure, with nominated persons responsible for implementing it as necessary, within, or outside of, normal working hours. Distribution records should be maintained, which will facilitate effective recall, and the written procedure should include emergency and off-hours contacts and telephone numbers (Sharp, 2005).

The complaints and defect report procedure is intended to be operated in conjunction with a "COMPLAINT/DEFECT REPORT" record (Figure 5), a copy of which, as is indicated, should form part of the SOP. Copies of this report form should be provided to all persons in the organization who may possibly be the first recipients of a complaint. They should be trained in its use and in the crucial importance of taking all such reports very seriously. As the complaints and defect report SOP indicates, if the complaints (etc.) procedure leads to a conclusion to recall (or freeze), then the recall (or freeze) procedure must be implemented. It is vital that this SOP is kept up to date, particularly in regard to internal and external names, addresses, and phone numbers, and that it is regularly shown (by "dummy runs") to be operable at any time. (The need to urgently recall does not arise only between 08.00 hours to 17.00 hours, Monday through Friday.)

As explained above the extent of recall, if required to do so depends on the distribution channel and record system of the company. In case of developed countries with well developed system of distribution records starting from the manufacturer up to the end user level, the recall procedure would be possible up to the end user. In such countries, the effective recall can protect patients, in cases of the product defects which may have severe adverse effect on the patient from use of the product if it is not recalled. However, the scenario of such recall procedure is very much alarming in case of developing countries where the distribution records of products are not traceable up to the end user, which needs to be recalled. Majority of the cases the distribution records are maintained up to the wholesaler, and/or retailer's level. In this scenario for serious cases, the recall procedure simply fails to achieve its goal to protect the end user from the impact of the effect. This needs to be strengthened by developing stringent regulatory requirements to have proper distribution record available up to the patient level for effective recall at the time of need. Otherwise the system of effective recall remains as SOP only.

COMPLAINT/DEFECT REPORT

Page 1 of 1

1. Date Complaint/Report received Time

2. Received by

3. Received from:

Name

Address:

Telephone number

Fax number

e-mail

4.Name/address/ phone numbers, etc. of other contacts/persons/organizations:

5. Product(s) involved:

6. Batch/lot numbers:

7. Name of complaint/report (attach any written correspondence)

8. Have samples been returned for examination? (Give details)

9. Are samples available for collection/examination? (Give details)

10. Results of investigations/Tests (attach other sheets as necessary)

11. Conclusions, and decision on action to be taken

Signed Date.....

12. Letter(s) sent toDate

13. Also considered necessary to inform: Done/Date:

14. Was decision taken to **FREEZE** (beyond own on-site stocks) or **Recall**?
IF "YES," RECALL (or FREEZE) SOP MUST BE IMPLEMENTED IMMEDIATELY

Signed

Date

Fig. 5. Complaint/Defect Report Record (Source: Sharp, 2005)

4.8 Contract production and analysis

The global industry is changing its shape through rationalization, mergers and acquisitions. Companies are increasingly considering the use of other manufacturers to produce or manufacture their products. Companies are also finding that they do not have the technology or expertise to manufacture certain new special dosage forms. In some cases, financial targets mean that companies are not using manufacturing as a core business process. This means that the importance of contract manufacturing and testing of products

is also increasing. The main principle underlying contract production and analysis is very simple. The work has to be clearly defined, agreed and controlled to avoid misunderstandings. The simplest way to avoid such misunderstandings is to have a written contract, setting out the duties of all parties to the contract and the standards that must be met. The standards of performance refer not only to product quality standards but also many other non-GMP aspects, e.g. relating to financial matters. It must be clear to everyone who is the authorized person, having the responsibility and the final authority to release a batch for sale. The contract should also specify clearly what would happen to materials that are rejected.

4.8.1 The contract giver (the client/company)

The contract giver is responsible for assessing the competence of proposed contract accepters that they will be able to do the work. It must assess whether the companies that offer to do the work really have the capability to do it. This evaluation must also include an assessment as to whether they are able to operate in accordance with the GMP principles. Once the conclusion has been reached that the contract accepter has not only the technical competence but also the GMP competence and then the contract giver must provide a full package of technical information to the contract accepter. This means that all the information relevant to personnel, premises and equipment must be provided. If there are hazards associated with cross-contamination of other products these must be highlighted. Finally, the product made or tested under the contract must only be released by the authorized person in compliance with the marketing authorization. In some cases the authorized person may be a designated staff member of the contract accepter if this responsibility is delegated in writing by the contract giver and if such delegation is permitted by national regulations.

4.8.2 The contract accepter (contractor)

The contract accepter also has responsibilities. The company must be competent to do the work. It means that it has the necessary facilities, premises and equipment, both in type and in quantity, to undertake the work. It must have a manufacturing authorization to do this type of work. This means that its staff has the necessary qualifications, training and experience to be able to do the work. The contract accepter may not pass the work or any part of it on to a (third) subcontractor party without the approval of the contract giver. Finally, once a contract accepter has signed the contract, it must not then undertake new work which might adversely affect the quality of the existing products. An illustration of this would be to take on manufacture a penicillin product in the same facility, as other products of the contract giver.

4.9 Self-inspection, quality audits and supplier's audits/approval

The purpose of self-inspection is to evaluate the manufacturer's compliance with GMP in all aspects of production and quality control. The self-inspection programme should be designed to detect any shortcomings in the implementation of GMP and to recommend the necessary corrective actions. Self-inspections should be performed routinely, and may be, in addition, performed on special occasions, e.g. in the case of product recalls or repeated

rejections, or when an inspection by the health authorities is announced. The team responsible for self-inspection should consist of personnel who can evaluate the implementation of GMP objectively. Management appoints a self-inspection team consisting of experts in their respective fields and familiar with GMP.

The frequency at which self-inspections are conducted may depend on company requirements but should preferably be at least once a year. A report should be made at the completion of a self-inspection. The report should include: (a) self-inspection results; (b) evaluation and conclusions; and (c) recommended corrective actions. All recommendations for corrective action should be implemented. The procedure for self-inspection should be documented, and there should be an effective follow-up programme. It may be useful to supplement self-inspections with a quality audit. A quality audit consists of an examination and assessment of all or part of a quality system with the specific purpose of improving it. A quality audit is usually conducted by outside or independent specialists or a team designated by the management for this purpose. Such audits may also be extended to suppliers and contractors.

The person responsible for QC should have responsibility together with other relevant departments for approving suppliers who can reliably supply starting and packaging materials that meet established specifications. Before suppliers are approved and included in the approved supplier's list or specifications, they should be evaluated. The evaluation should take into account a supplier's history and the nature of the materials to be supplied. If an audit is required, it should determine the supplier's ability to conform to GMP standards (WHOTRS 961, 2011).

The practice of supplier audit is difficult to conduct specially when the suppliers are in distance from the auditing company and/or the requirement of the auditing company are not of significant in values where is supplier is not interested with the party to do the business. This difficulty arises with the companies operating in developing countries with small business volume. With small business volume, the company's requirements are such that the process of conducting supplier audit shall be a costly affair in one end and the supplier shows not interest in the other end. In such cases, an alternative ways need to find out for supplier approval. In such case the suppliers are approved based on their history and list of customers of the suppliers. Another approach may be to form a group of all small companies together so that the quantities required in common are pulled together to create interest on the supplier for the business. All the companies in together can have an audit for approval of the supplier. In such cases of difficulty in supplier approval, all the initial supplies made are subjected for 100% sampling and test before approval of the material supplied.

4.10 Personnel, training and personal hygiene

The quality of a product ultimately depends on the quality of those producing it....

- Sir Dereck Dunlop (1971)

The establishment and maintenance of a satisfactory system of quality assurance and the correct manufacture and control of pharmaceutical products and active ingredients rely upon people. For this reason there must be sufficient qualified personnel to carry out all the

tasks for which the manufacturer is responsible. Individual responsibilities should be clearly defined and understood by the persons concerned and recorded as written job descriptions (WHOTRS 961, 2011). Personnel should be aware of the principles of GMP that affect them and receive initial and continuing training, including hygiene instructions, relevant to their need (Sharp, 2005). In order to effectively monitor and control virtually all GMP documents/activities in a facility, the quality professional should have a very high level of knowledge, skills, and experience. Figure 6 represents a comprehensive list of the knowledge and skills needed for high level quality professional in the 21st century (Nally, 2007).

It is the people (the “men” – the human species, not the gender – or the personnel) that are the most important factor in the assurance of quality. This is true of all levels within an organization, from company president and managing director to the most-junior employee. It may well be possible (if not altogether desirable) for high-quality, well-trained, dedicated personnel to compensate for a lack or deficiency in the other elements. Nothing, not even the finest premises, equipment, materials, or procedures can compensate for the quality hazard represented by low-standard, ill-trained, or poorly motivated staff. Self-responsible, well-motivated staff will produce more goods, with a greater assurance of the quality of those goods, than will poorly motivated staff. Conversely, in the special context of medicines manufacture, poorly motivated staff can represent a hazard to themselves, to the public, and to company profits (Sharp, 2005).

4.10.1 Training system

Because the quality of the product is directly affected by actions that personnel take in their jobs, there must be assurance that they are properly trained. This assurance is built by having a training system that is robust, compliant, and sustainable and is able to produce individuals who are qualified (Nally, 2007). Elements that are needed in a strong training system include the following: an accurate description of the job or role; specific training requirements for each job or role; training plan to accomplish the training; training materials that are applicable to each type of training; qualified trainers to perform the training; evaluations to measure the effectiveness of the training; and a documentation and record keeping system for storage and retrieval of training records and materials.

Job Description: A job description should define the job and role of the individual. It should be fairly high level and include major job functions, not tasks the individual performs. The function may be divided into duties and responsibilities, competencies that an individual may have, and prerequisites needed (e.g., must be a college graduate, must have five years of experience, etc.). The manager is expected “to define appropriate qualifications for each position to help ensure individuals are assigned appropriate responsibilities.”

Training Requirement: When a job description has been created and approved by both human resources and the functional area, training requirements can then be defined. The knowledge and skills the individual needs to successfully perform the job should be identified. The desired skills and knowledge are compared against the individual’s skills and knowledge when entering the position; gaps are identified. The training requirements will be derived from the identified gaps. Training requirements must be updated on a periodic basis. Training requirements should be established for all levels within the organization.

Business Knowledge/Understanding <ul style="list-style-type: none">• Policies/Standards/Regulations• Manufactured Products• Pharm/Bio Industry Knowledge (Rx, OTC) – local• Global• General Business (Mfg., Logistics, TS, Eng.)• HR, Finance, Marketing/Sales, IS	Manufacturing <ul style="list-style-type: none">• Formulation & Manufacturing Procedures• Statistical Process Controls• Process Capability• Equipment & Processing Parameters• Environmental Monitoring
Leadership & Management Skills <ul style="list-style-type: none">• Facilitation and Training• Positive Regard and Motivation• Performance Assessment/Feedback/Coaching• Team Building• Networking	Chemistry/Microbiology <ul style="list-style-type: none">• Good Laboratory Practices• Latest Instrumentation & Automation• LIMS or Lab Management system• Methods Development• Methods Validation
Communication Skills <ul style="list-style-type: none">• Oral• Written• Presentation• Influencing• Negotiation and Conflict Management• Language	Audit/Assessment (Auditor) Skills <ul style="list-style-type: none">• Pharmaceutical/Biological Operations• Packaging Materials Operations• Bulk Pharmaceutical Chemical (BPC) Op.• ISO 9000• Process/System Approach
Process Skills <ul style="list-style-type: none">• Time Management• Quality Planning• Proposal Preparation• Project Management & Planning• Process Management• Change Management• Problem Solving/Decision making• Management Tools• Risk Analysis & Management	Suppliers/Contractors/Third Parties <ul style="list-style-type: none">• Quality Assurance of Suppliers• Quality Assurance of Third Parties• Partnership Management
Quality Design & Prevention <ul style="list-style-type: none">• Basic Quality Tools• Process Capability and Statistical QC• Process/System Design• Design of Experiments (DOE)• Failure Mode Effect Analysis (FMEA)• Value Engineering/ Analysis & Re-Engineering• Benchmarking	Quality Systems <ul style="list-style-type: none">• Policies/Procedures• Annual Product Review (APR)• Complaints• Failure Investigations/Materials Decisions• Product Release• Change Control• Components, Materials/Warehousing/Dist.• Calibration & Maintenance• Management Notification• Training• Recall• Technology Transfer
Validation <ul style="list-style-type: none">• Facilities/Critical Plant Systems (IQ/OQ/PQ)• Production Equipment (IQ/OQ/PQ)• Manufacturing Process Validation• Retrospective Process Validation (data review)• Equipment Cleaning Validation• Computer System Validation	Customer Awareness/Understanding <ul style="list-style-type: none">• Complaint Handling• Product Audits/Competitive Comparisons• Customer Visits/Interviews• Market/Customer Surveys• Next Operation as Customer (NOAC)• Six Sigma Approach

Fig. 6. Knowledge and Skill Requirements for Today’s Quality Professional (Source: Nally, 2007)

Training Plan: To ensure that the individual receives the “right” training at the “right” time, an individual training plan should be created and executed for each individual. The individual’s curriculum should include procedural (knowledge) training, usually SOPs, and competency-based skills training (on-the-job training or OJT). Both these types of training should be standardized as much as possible with the same training material used for all trainees. The individual’s curriculum will include different levels of training. These can be divided into three levels. The first level is an overview or general training conducted by the site HR or corporate training group as part of a new hire or induction training. The second level is held within the functional area. The third level, most specific to the employee, is one-on-one training (Figure 7). The training plan should include an approximate training time. The site may have an annual or semi-annual training plan that defines what GMP training should be given to functional areas at the site and when.

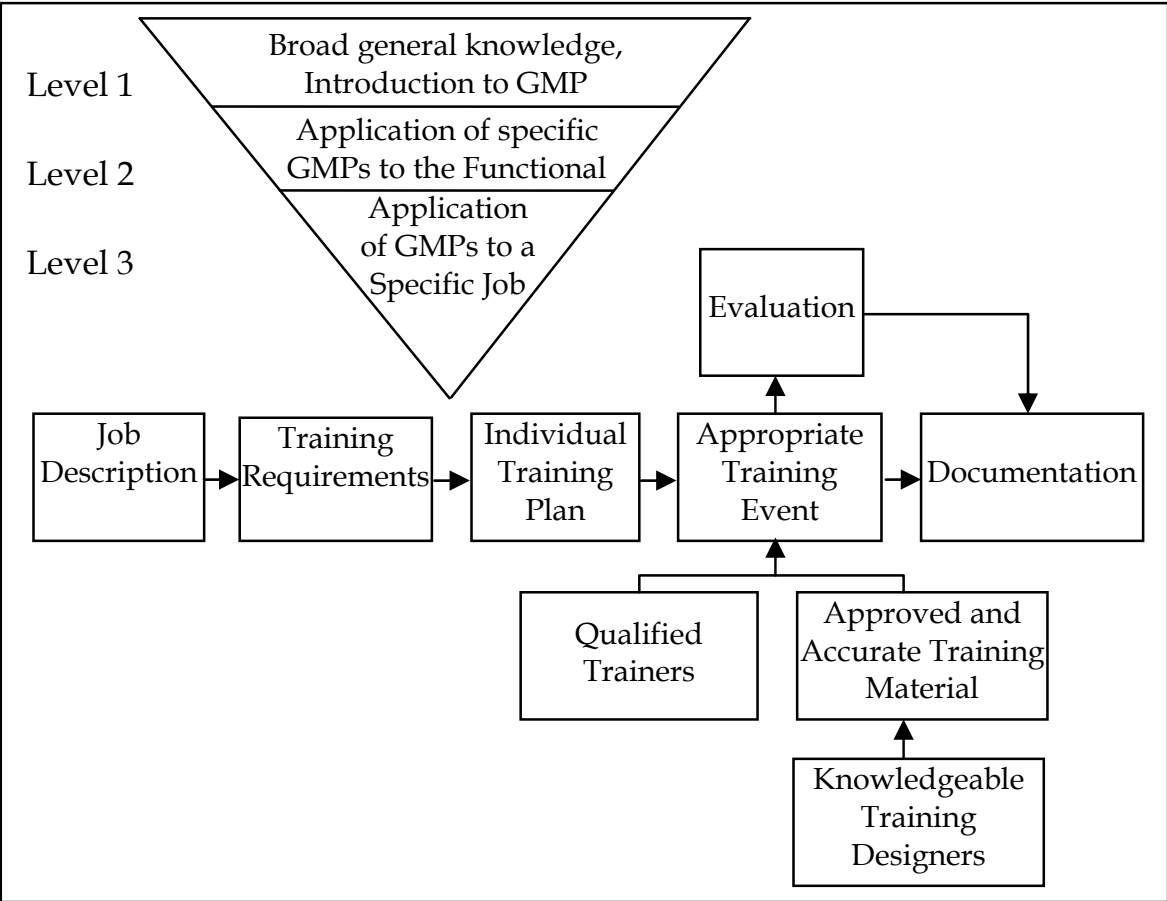


Fig. 7. Training System (Source: Nally, 2007)

Training Materials: Training materials should be designed and developed for most training. Whether the training is given once or many times, the information should be the same. The training material should be clear and well organized. Training materials should contain stated objectives. In addition to the content being trained, the reason behind the training should be explained and stressed. If training GMPs, the impact of the particular training on the production of the product should be explained.

Qualified Trainers: GMP training to be given by qualified personnel, the company should have a procedure and process for qualifying trainers. Minimum requirements for trainers

may include some formal education (e.g., Train-the-Trainer course) or experience in presenting training, subject matter expertise in the subject they will be training, understanding of GMPs in terms of how it impacts the specific training they are responsible for, and the knowledge about how to train adults. Trainers should be selected for their ability to help individuals learn. If they are on-the-job trainer, they should be able to demonstrate the skills and also clearly explain how to perform the skill.

Evaluation, Documentation/Record Keeping: Job skills and GMP training should be evaluated. For GMP training, evaluation tools such as questionnaires, case studies, discussions, and other tools may be used. For job skills, a performance-based evaluation is used. The usual method is to have an observer watch the individual in training and complete a checklist. The individual should be able to demonstrate the correct practice without the coaching or help from another individual. The performance checklist is usually signed by the trainee and by a member of management. This document is retained. Evaluations should be performed after the training. The training system and training processes should be documented, possibly in an SOP, describing how the training system works and the type of training included in the training system. Training records should be retained in a documentation system. There should also be a method to ensure that training curricula and training requirements are up-to-date in the event that an individual transfers to another job within the company. Any changes made to curricula should be documented and approved. Training documentation should be readily retrievable (Nally, 2007).

There should be two types of training records:

1. The personal file of each member of staff should contain a record of the training received, indicated by module reference number (see Figure 8).
2. Departmental training records should be maintained, indicating in tabular form the training received by each member of staff (see Figure 9).

ABC Company

Personal Training Record

Name: Date Joined Company.....

Job Title:

1.

2.

3.

Training Record (module ref. and title)

Date

Fig. 8. Personal Training Record (Source: Sharp, 2005)

Name	GI/1	GI/2	GMP/1	GMP/2	GMP/3	GMP/4	GMP/5	STT/1	STT/2

Fig. 9. Company Training Record (Source: Sharp, 2005)

The concept of personal hygiene is described in the subheading of Sanitation and hygiene.

4.11 Premises

Premises must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out. The layout and design of premises must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products. Although the most important single factor in the assurance of the quality of medicinal products is the quality of the people who manufacture them, the premises in which they are manufactured will also have an important bearing on the quality of those products (Sharp, 2005). Pertinent consideration should be made prior to the selection of location for construction of pharmaceutical premises or alteration of existing facilities to ensure that the surrounding neighborhood is free from unsanitary environmental condition.

The choices of materials of construction for manufacturing facilities are numerous. Some examples are presented subsequently.

a. Walls. Walls in manufacturing areas, corridors, and packaging areas should be of plaster finish on high-quality concrete blocks or gypsum board. The finish should be smooth, usually with enamel or epoxy paint. They should be washable and able to resist repeated applications of cleaning and disinfecting agents. Internally, there should be no recesses that cannot be cleaned, and a minimum of projecting ledges, shelves, fixtures and fittings.

b. Floors. Floor covering should be selected for durability as well as for cleanability and resistance to the chemicals with which it is likely to come into contact. Terrazzo provides a hard-wearing finish; both tiles and poured-in-place finishes are available. The latter is preferable for manufacturing areas; if tiles are used, care must be taken to ensure effective sealing between the tiles, which, otherwise, could become a harboring area of dirt and microorganisms. Welded vinyl sheeting provides an even, easy to clean surface. Epoxy flooring provides a durable and readily cleanable surface. However, the subsurface finish is extremely important. Where drains or drainage gullies are installed, they should be easily cleanable and trapped to prevent reflux.

c. Ceilings. Suspended ceilings may be provided in office areas, laboratories, toilets, and cafeterias. They usually consist of lay-in acoustical panels of non brittle, non friable, non asbestos and non combustible material. Manufacturing areas require a smooth finish, often of seamless plaster or gypsum board. All ceiling fixtures such as light fittings, air outlets and returns should be designed to assure ease of cleaning and to minimize the potential for accumulation of dust.

d. Services. In the building design, provisions must be made for drains, water, steam, electricity, and other services to allow for ease of maintenance. Access should, ideally, be possible without disruption of activity within the actual rooms provided with the services.

Doors and window-frames should all have a smooth, hard, impervious finish, and should close tightly. Window and door frames should be fitted flush, at least on sides facing inward to processing areas. Doors, except emergency exits, should not open directly from production areas to the outside world. Any emergency exit doors should be kept shut and sealed, and designed so as to be openable only when emergency demands. Despite the

space-saving advantages, sliding doors should be avoided because of the difficulty of maintaining the sliding gear in a clean condition.

The layout design of the facility must minimize the possibility of mix-ups or contamination. Sufficient space must be provided to allow adequate separation of adjacent equipment and operations. An example of this includes the spatial separation of packaging lines so that packaging components, bulk product, and finished product cannot intermix between lines and that dust or spillage from one line cannot result in the contamination of adjacent equipment. For example, a common practice is to introduce a physical barrier between the packaging lines. The layout of the manufacturing and support operations must account for efficient material, personnel, and equipment flow patterns. Adequate access control is required to restrict entrance to manufacturing areas. The most efficient and compliant flow pattern is the one that provides for unidirectional flow.

Temperature and humidity need to be controlled primarily for the comfort of operators. The gowning requirements to minimize the potential for microbial contamination from operators are rather stringent and can easily cause personal discomfort, which could, in turn, adversely impact on the aseptic processing. Conditions in the order of 68°F /20°C (65°F/18°C -70°F/21°C) and 45% (40%-50%) relative humidity have been found to be suitable. Independent of gowning requirements, relative humidity ranges must be carefully selected. Continuous relative humidity levels below 15% can cause static electricity discharge and health concerns and levels above 60% can be the source of microbial growth and corrosion (Signore & Jacobs, 2005).

4.11.1 Layout concepts

A very basic block design showing a simple single-storey linear flow layout is given in Figure 10. The internal building requirements vary according to the nature of the operations carried out or type of product produced within the various departments, sections, or rooms (Sharp, 2000). Within the facility there will be various flow-patterns. These flows will be principally of materials and products, and of personnel. Materials will be received, held pending test, released for use, held in store, dispensed for manufacture, and processed into products that are then packaged, tested, and held in quarantine pending release, and then stored pending distribution.

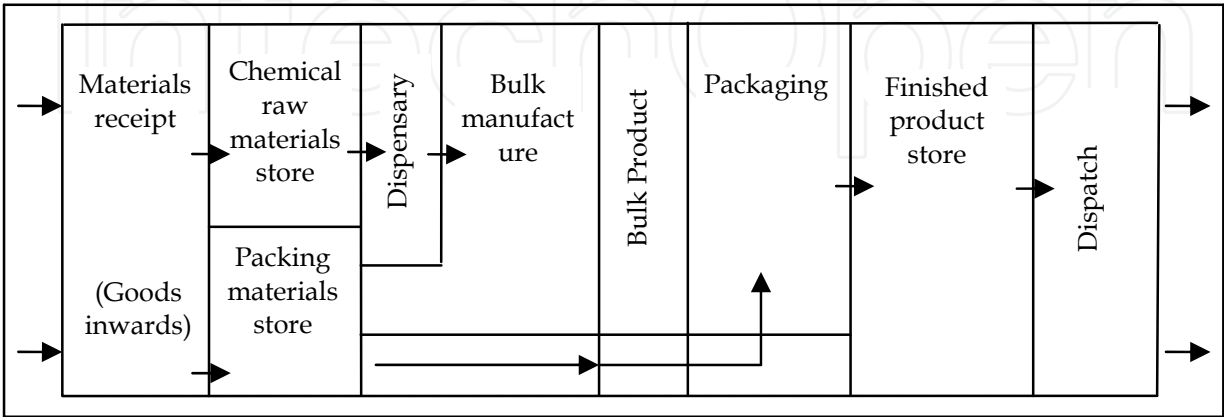


Fig. 10. Simple Single-Story Linear Flow Pattern for Pharmaceutical Manufacturing. Sampling Quarantine and Release Stages not shown. Not a scale (Source: Sharp, 2000)

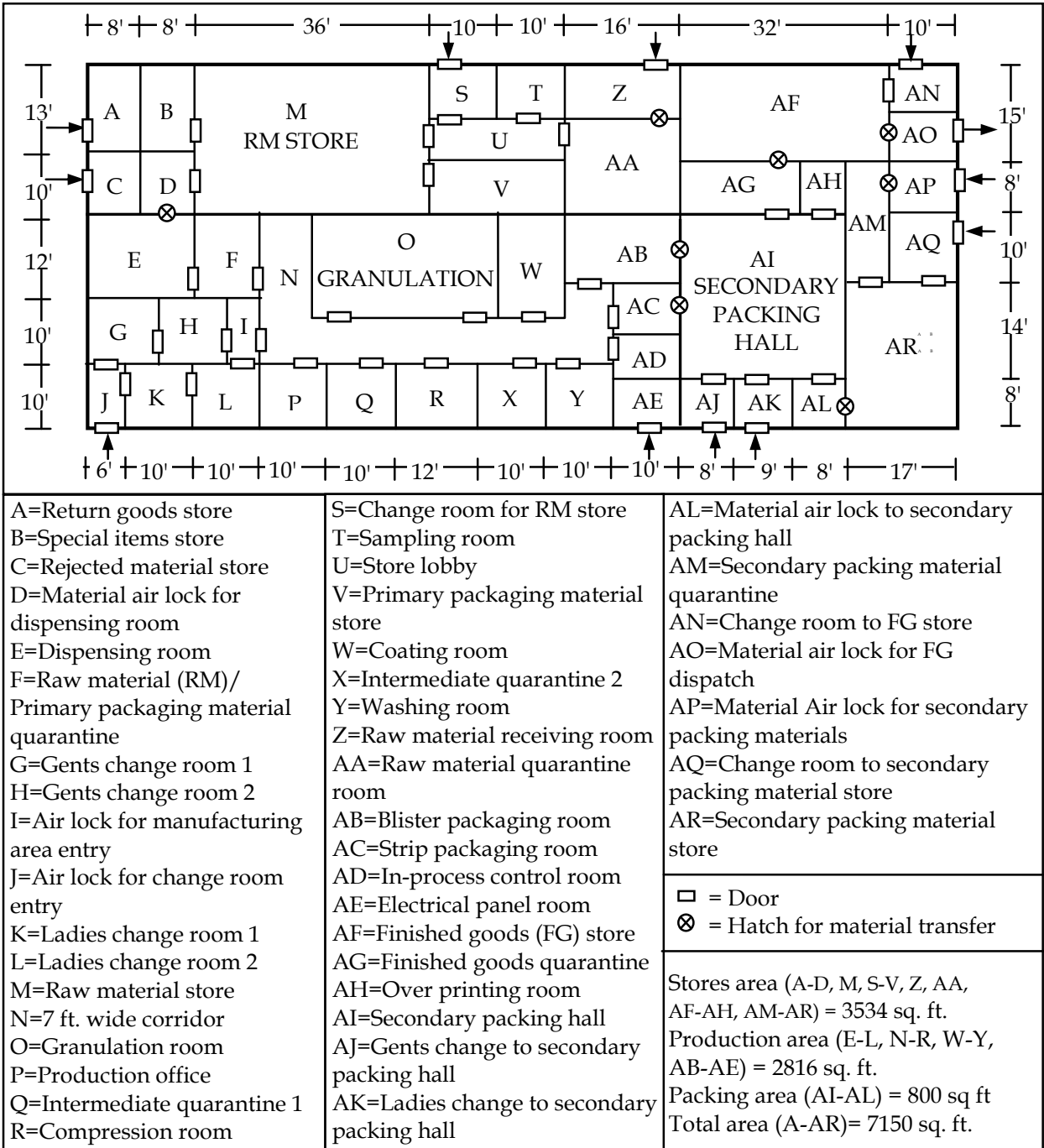


Fig. 11. Single-Story Linear Flow Pattern for a Tablet Manufacturing Unit (Detail Design)
QC Area is not shown. Not a Scale

A horizontal layout plan for manufacturing tablet dosage form with detail drawing is shown in Figure 11. The layout is considered as the smallest possible design of 7150 sq. ft. area covering all requirements of manufacturing and packaging including stores area for a tablet manufacturing unit. The design does not cover QC and other supporting areas such as canteen, engineering and/or administration rooms.

Most of the required pipe works are taken from inside the wall in concealed manner. Exposed pipelines should not touch walls but be suspended from or be supported by

brackets, sufficiently separated to allow through cleaning. The pipe works at exposed surfaces are required to be clearly marked with direction flow of the utilities used. In general all the exposed pipelined inside the processing area is made of SS 304 grade with exception of SS 316L for those used in supply of purified water. Different colour codes are used for identification of the utility pipe lines (Table 3).

Utility used	Pipe colour code	Colour of letter for legend
Pressurized steam	Red	Black
Compressed air	Orange	Black
Vacuum	Yellow	Black
Nitrogen	Grey	Black
Oxygen	Light Blue	Black
LPG	Dark Green	Black
Carbon dioxide	Violet	Black
Distilled water (water for injection)	White	Black
Deionized water	Light Green	Black
Well water/ water for fire fighting	Black	White

Table 3. Identification of Pipelines (Source: ASEAN, 2000)

A manufacturing facility, built and finished as designed, still requires various other inputs, in addition to people, equipment, and materials, before the manufacture of products can begin. These can be referred to collectively as “plant services, systems, and utilities.” Heating, ventilation, and air-conditioning (HVAC), Lighting, Water for pharmaceutical use (WPU), Electricity and Gases/Compressed air are considered as the major plant services, systems and utilities requirements for a pharmaceutical unit.

4.11.2 Heating, Ventilation and Air-Conditioning (HVAC)

“Natural” ventilation (via doors and windows) is not acceptable in medicine manufacturing area because of the risk of product contamination from the outside world (particulate matter, dust, dirt, microorganisms, insects, etc.). Control of humidity is also important for a number of products, particularly effervescent products. Windows from production areas to the outside world should thus normally remain closed, and preferably not be openable. External doors should be air locked, or only openable in an emergency. Therefore, some form of forced; conditioned, usually filtered, air supply is required with proper heating, ventilation and air-conditioning (HVAC) system (WHOTRS 937, 2006).

HVAC play an important role in ensuring the manufacture of quality medicinal products. A well designed HVAC system will also provide comfortable conditions for operators. HVAC system design influences architectural layouts with regard to items such as airlock positions, doorways and lobbies. The architectural components have an effect on room pressure differential cascades and cross-contamination control. The prevention of contamination and cross-contamination is an essential design consideration of the HVAC system. In view of these critical aspects, the design of the HVAC system should be considered at the concept design stage of a pharmaceutical manufacturing plant.

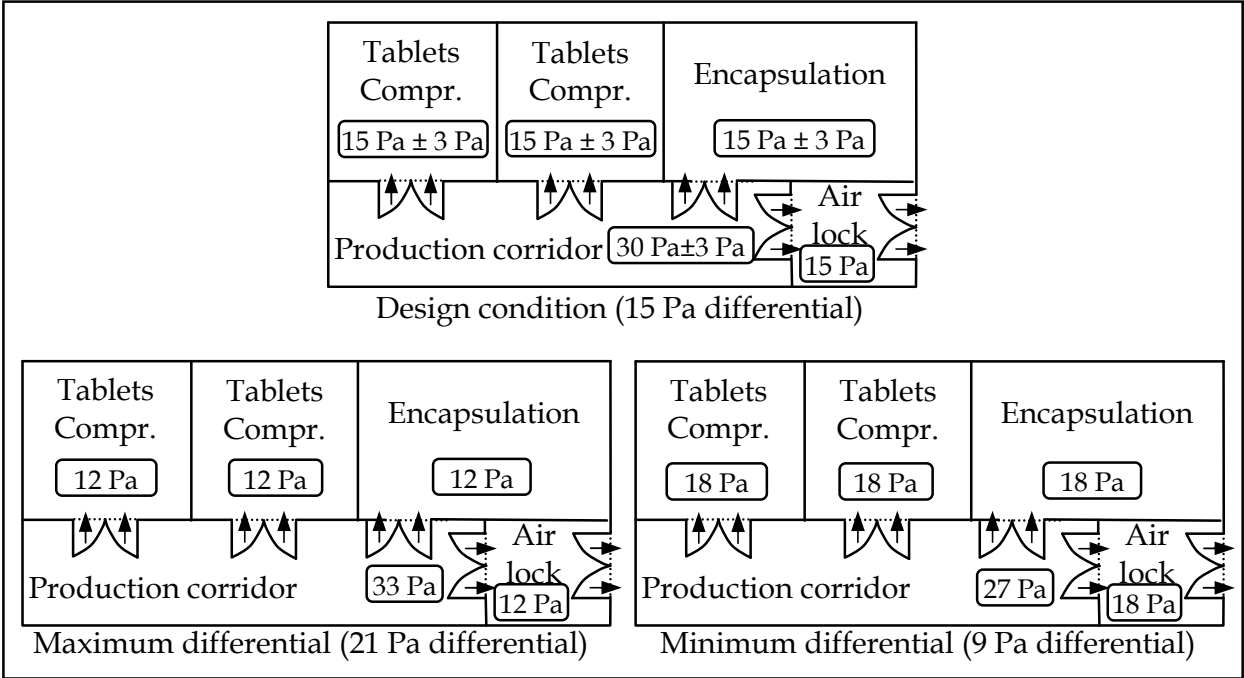


Fig. 12. Examples of Pressure Cascade (Source: WHOTRS 937, 2006)

While designing the HVAC system following parameters are required to be considered for operation of oral solid dosage (OSD) formulations avoiding cross contamination. The operating room should be of Class 100000 condition. The dispensing room used for weighing raw materials and sampling room used for raw material sampling for testing should be provided with reverse laminar air flow system with Class 100 condition. The most widely accepted pressure differential for achieving containment between two adjacent zones is 15 Pa, but pressure differentials of between 5 Pa and 20 Pa may be acceptable (WHO TRS 937, 2006). The door in the room should always open towards the high pressure area (Figure 12). The air changes per hour in the operating room that is the times the volume of air supplied per hour in comparison to the volume of room should be at least 20 per hour. In general room temperature and humidity maintained at 22±3°C and 50±5% respectively have been found to be suitable for personal comfort.

The HVAC system may be designed either with 100% fresh air system or with 85-90% reticulated air system. In case of recirculation system the supply air stream is to be provided with high-efficiency particulate air (HEPA) filters to remove contaminants, and thus prevent cross-contamination. Recirculated air should not be used if there are no HEPA filters installed in the system, unless the air handling system is serving a single product facility. In case of 100% fresh air system the degree of filtration on the supply air and exhaust air should be determined depend on the level of cleanliness required; exhaust air contaminants and local environmental regulations. The required degree of air cleanliness in most OSD manufacturing facilities can normally be achieved without use of HEPA filters. In locations with different climatic conditions, difference between a systems operating on 100% fresh air versus a system utilizing recirculated air with HEPA filtration should be considered in the context of cost of installation as against operating cost.

4.11.3 Lighting

Lighting levels should be adequate to permit operators to do their work properly, accurately, and attentively. Lighting of production and packaging areas should be sufficiently bright to enable good vision (Table 4). Although daylight is preferable from a number of aspects, it needs to be noted that a number of pharmaceutical products and materials are affected by UV light. The design and layout of a modern pharmaceutical factory also usually make artificial lighting inevitable. It should be installed so as not to create uncleanable dust traps, e.g., preferably flush-fitted to the ceiling, or with smooth easily accessible and cleanable surfaces. To avoid photo degradation, a suitable light using sodium vapor lamp is to be provided with dispensing/sampling booth for weighing/sampling of highly light sensitive materials.

Illumination intensity (in Lux)	Specific Area
20	- narrow corridor, aisle
50	- warehouse for big size containers, corridor for personal traffic
100	- corridor for traffic of personnel and forklift, break room, locker rooms, rest rooms, utility rooms, staircase lobby
200	- workshop, warehouse
300	- laboratory
500	- offices with reading activities, production room, first aid room
750	- draft room
1000	- visual inspection
1 foot candle = 1 lumen/ feet ² = 10.764 lux (ft.c) lm/ ft ²	

Table 4. The Recommended Illumination in Premises (Source: ASEAN, 2000)

4.11.4 Water for Pharmaceutical Use (WPU)

Water is the most widely used substance in the production, processing and formulation of pharmaceutical products. It has unique chemical properties due to its polarity and hydrogen bonds. This means it is able to dissolve, absorb, adsorb or suspend many different compounds. These include contaminants that may represent hazards in themselves or that may be able to react with intended product substances, resulting in hazards to health (WHOTRS 929, 2005).

Different grades of water quality are required depending on the route of administration of the pharmaceutical products. Control of the quality of water throughout the production, storage and distribution processes, including microbiological and chemical quality, is a major concern. Unlike other product and process ingredients, water is usually drawn from a system on demand, and is not subject to testing and batch or lot release before use. Assurance of quality to meet the on-demand expectation is, therefore, essential. Additionally, certain microbiological tests may require periods of incubation and, therefore, the results are likely to lag behind the water use. Control of the microbiological quality of WPU is a high priority. Some types of microorganism may proliferate in water treatment components and in the storage and distribution systems. It is very important to minimize

microbial contamination by routine sanitization and taking appropriate measures to prevent microbial proliferation (WHOTRS 929, 2005).

Pharmaceutical water production, storage and distribution systems should be designed, installed, commissioned, validated and maintained to ensure the reliable production of water of an appropriate quality. Where chemical sanitization of the water systems is part of the biocontamination control programme, a validated procedure should be followed to ensure that the sanitizing agent has been effectively removed. Steam sanitization is considered as one of the best alternative for WPU system. Water may be originally obtained from a number of sources. Water from wells or bore-holes, given suitable treatment, has been used to manufacture pharmaceuticals. In many countries, the most usual source is normal mains, or town, water of potable (drinkable) quality. For pharmaceutical purposes, it may be considered that there are four basic grades of water:

Drinking Water is unmodified except for limited treatment of the water derived from a natural or stored source. Examples of natural sources include springs, wells, rivers, lakes and the sea. The condition of the source water will dictate the treatment required to render it safe for human consumption (drinking). It is common for drinking-water to be derived from a public water supply that may be a combination of more than one of the natural sources listed above. Typical processes employed at a user plant or by a water supply authority include: filtration, softening, disinfection or sanitization (e.g. by sodium hypochlorite (chlorine) injection), iron (ferrous) removal, precipitation, and reduction of specific inorganic/organic materials.

Purified Water (PW) should be prepared from a potable water source as a minimum-quality feed-water, should meet the pharmacopoeial specifications for chemical and microbiological purity, and should be protected from recontamination and microbial proliferation. There are no prescribed methods for the production of PW in the pharmacopoeias. Any appropriate qualified purification technique or sequence of techniques may be used to prepare PW. Typically ion exchange, ultra filtration and/or reverse osmosis processes are used. Electrodionization or Distillation can also be used. Ambient-temperature PW systems are especially susceptible to microbiological contamination, particularly when equipment is static during periods of no or low demand for water. It is essential to consider the following mechanisms for the efficient control of contamination.

- The headspace in the storage vessel is an area of risk where water droplets and air can come into contact at temperatures that encourage the proliferation of microbiological organisms. The water distribution loop should be configured to ensure that the headspace of the storage vessel is effectively wetted by a flow of water. The use of spray ball or distributor devices to wet the surfaces should be considered.
- Nozzles within the storage vessels should be configured to avoid dead zones where microbiological contamination might be harboured.
- Vent filters are fitted to storage vessels to allow the internal level of liquid to fluctuate. The filters should be bacteria-retentive, hydrophobic and ideally be configured to allow in situ testing of integrity. Offline testing is also acceptable.
- Where pressure-relief valves and bursting discs are provided on storage vessels to protect them from over-pressurization, these devices should be of a sanitary design.
- Maintenance of continuous turbulent flow circulation within water distribution systems reduces the propensity for the formation of biofilms.

- For ambient temperature systems, pipework should be isolated from adjacent hot pipes. Deadlegs in the pipework installation greater than 1.5 times the branch diameter should be avoided.
- Pressure gauges should be separated from the system by membranes.
- Hygienic pattern diaphragm valves should be used.
- Pipework should be laid to falls to allow drainage.
- The growth of microorganisms can be inhibited by: ultraviolet radiation sources in pipe work; maintaining the system heated (guidance temperature 70–80 °C); sanitizing the system periodically using hot water (guidance temperature >70 °C); sterilizing or sanitizing the system periodically using superheated hot water or clean steam; and routine chemical sanitization using ozone or other suitable chemical agents. When chemical sanitization is used, it is essential to prove that the agent has been removed prior to using the water. Ozone can be effectively removed by using ultraviolet radiation.

4.11.5 Electricity

In general the electricity supply is made through concealed wiring with five wires (three phase wires, one neutral wire and one ground wire) for three-phase connections and three wires (one phase wire, one neutral wire and one ground wire) for single-phase connections using suitable size wires. Conductors of a three-phase system are usually identified by a color code, to allow for balanced loading and to assure the correct phase rotation for induction motors. Colors used may adhere to International Standard IEC 60446, older standards or to no standard at all and may vary even within a single installation. For example, in the U.S. and Canada, different color codes are used for grounded (earthed) and ungrounded systems (Wikipedia. (2012b)). In case of India, Pakistan and Nepal, generally red, yellow and blue color wires are used for three phases L1, L2 and L3 connections, black for neutral and green for ground connections.

Continuity of electricity supply is essential for a number of systems or processes (air supply and extraction, particularly for sterile manufacture; fermentation plants; incubators; stability chambers) and thus backup systems should be available in the event of mains failure. Ideally, there should be automatic changeover and reset from mains to emergency generator supply. Certain equipment (computers, microprocessor control systems, some analytical instruments) may need voltage stabilization in order to operate reliably (Sharp, 2005).

4.11.6 Gases/compressed air

Various gases may be used for a variety of purposes, for example, inert gases used as a protective “blanket” or to displace air in an ampoule head-space, as propellants in aerosol products, as sterilants (e.g., ethylene oxide), as a source of flame in glass ampoule sealing. Any gas that may come into contact with a product (or product contact surfaces), or that is used in the manufacture of a product, must be treated as if it were a raw material and must therefore be subject to standard quality control procedures to ensure that it conforms to predetermined quality standards. A number of gases are used in laboratory test procedures. If these are not of the required or specified quality, then the reliability of the test results may suffer. Gas pipelines, from cylinders or from bulk gas storage, should be clearly marked as

to contents. It should not be possible to switch pipelines and connections and thus to supply the wrong gas. Dedicated, pin-indexed valves and connections, as (one hopes) used in hospital gas supply lines, should be employed where possible.

Gases (including compressed air) may need to be filtered when supplied to production areas generally. Gases (including compressed air), when supplied to sterile products manufacturing areas (and other controlled environments), will certainly need to be filtered (as close to the point of use as possible) to ensure that they conform to the particulate and microbial standards for the area (Sharp, 2005). In general the compressed air coming in contact with OSD products is recommend to be oil and moisture free with particulate matter filtered through initial coarse and terminal 1 μ filters.

4.12 Equipment

Manufacturing equipment should be capable of producing products, materials, and intermediates that are intended and that conform to the required or specified quality characteristics. Furthermore, the equipment must be designed and built so that it is possible (and relatively easily possible) to clean it thoroughly. Surfaces that come into contact with products should have smooth, polished finishes, with no recesses, crevices, difficult corners, uneven joints, dead-legs, projections, or rough welds to harbor contamination or make cleaning difficult. Equipment must also be capable of withstanding repeated, thorough cleaning. Traces of previous product, at levels that might be acceptable in other industries, are totally unacceptable in the manufacture of medicines.

As far as the properties of the materials of construction of the equipment are concerned, there are two major concerns:

1. The possibility of contamination, or degradation, of the product by the material from which the equipment is constructed
2. The action of the product, or material in-process, on the material from which the equipment is constructed

Contamination of product can arise from shedding or leaching of contaminants from the equipment into the product or from reaction between the product and the material of the equipment. It is worth remembering that there are two aspects of the potential release of product contaminants by equipment: they could be toxic to patients, even in very small amounts, and they could cause product decomposition. As an example of the latter – penicillin can be inactivated by trace heavy metals.

Fixed equipment should be installed, piped in, and supplied with services in a manner that creates a minimum of recesses, corners, or areas that are difficult for cleaning. The equipment should be designed and located to suit the processes and products for which it is to be used. It must be shown to be capable of carrying out the processes for which it is used (that is, it should be properly commissioned, or “qualified”) and of being operated to the necessary hygienic standards. It should be maintained so as to be fit to perform its functions, and it should be easily and conveniently cleanable, both inside and out. Parts that come into contact with materials being processed should be non reactive or absorptive with respect to those materials. Equipment should be kept and stored in a clean condition and checked for cleanliness before each use.

Between batches (or “campaigns”) all manufacturing equipment must be thoroughly cleaned and (as necessary) disinfected or sterilized. There should be written procedures for doing this, which must be followed exactly. The cleaning program consists of two parts—the validation of the processes and detergents/sanitization agents and the day-to-day use of the validated processes and qualified detergents and sanitizers. Many cleaning processes are automated. These falls into two classes: clean in place (CIP) and clean out of place (COP). The CIP systems have their equipment provided with hard-piped services with cleaning solutions. The cleaning process is automated and usually is documented through a printout of the automation system. The COP systems consist of bringing the equipment to a cleaning station or placing the equipment in an automated washer.

Effectiveness of cleaning is a function of a number of factors, including time, temperature, and rate of turbulent flow of the cleaning solution; the concentration of chemical cleaning agents in the cleaning solution; and the surface finish (smoothness or roughness) of the surfaces to be cleaned. All these factors interact. For example, all other things being equal, it will take a longer time to completely clean a relatively rough internal surface as compared to a high-polish, smooth one. Higher temperatures will need lower times and flow rates, and so on. Cleaning solutions commonly employed contain caustic agents and detergents, and it must be remembered that, before cleaning is complete, it is necessary to ensure removal of the cleaning agents themselves. That is, there must be a rinsing stage, using (for aqueous products) water of a quality appropriate to, and compatible with, the products to be manufactured in the equipment.

4.13 Materials

A flow diagram illustrating the ordering, receipt, sampling, approval (or rejection), and dispensing of starting materials is shown in Figure 13. The purchasing department orders the material on the basis of a starting material specification provided to them by the QC. Purchasing department sends the order to an approved supplier, which is a company that has been approved, jointly by the QA, QC and production to supply the material in question. To continue with the flow-diagram, at the time of placing the order, the purchasing department sends a copy of the purchase order to the goods inwards (or receiving) department, where it is (accessibly) retained, pending the receipt of the goods.

On receipt, the goods are carefully examined by a responsible member of the goods inwards department for general condition, and to check for any signs of external damage, soiling, or dampness. At the same time, the labeled identity of the delivered material is checked and compared with the goods inwards copy of the purchase order, and with any supplier's delivery, or advice note, to confirm that the material delivered is, as far as its labeling is concerned, the material that was ordered. A check is also made at this time on all the identity labels on the containers in a multi container delivery. Different suppliers' batches within one delivery are to be segregated, one from another, with a different internal lot number for each entered on the QUARANTINE label, which is applied to each container. If all the containers in the delivery appear to be correct and in good condition, the goods inwards department then place on each container a QUARANTINE label (see Figure 14), with the entries for “Code Number,” “Name of Material,” “Lot Number,” and “Date Received” are completed.

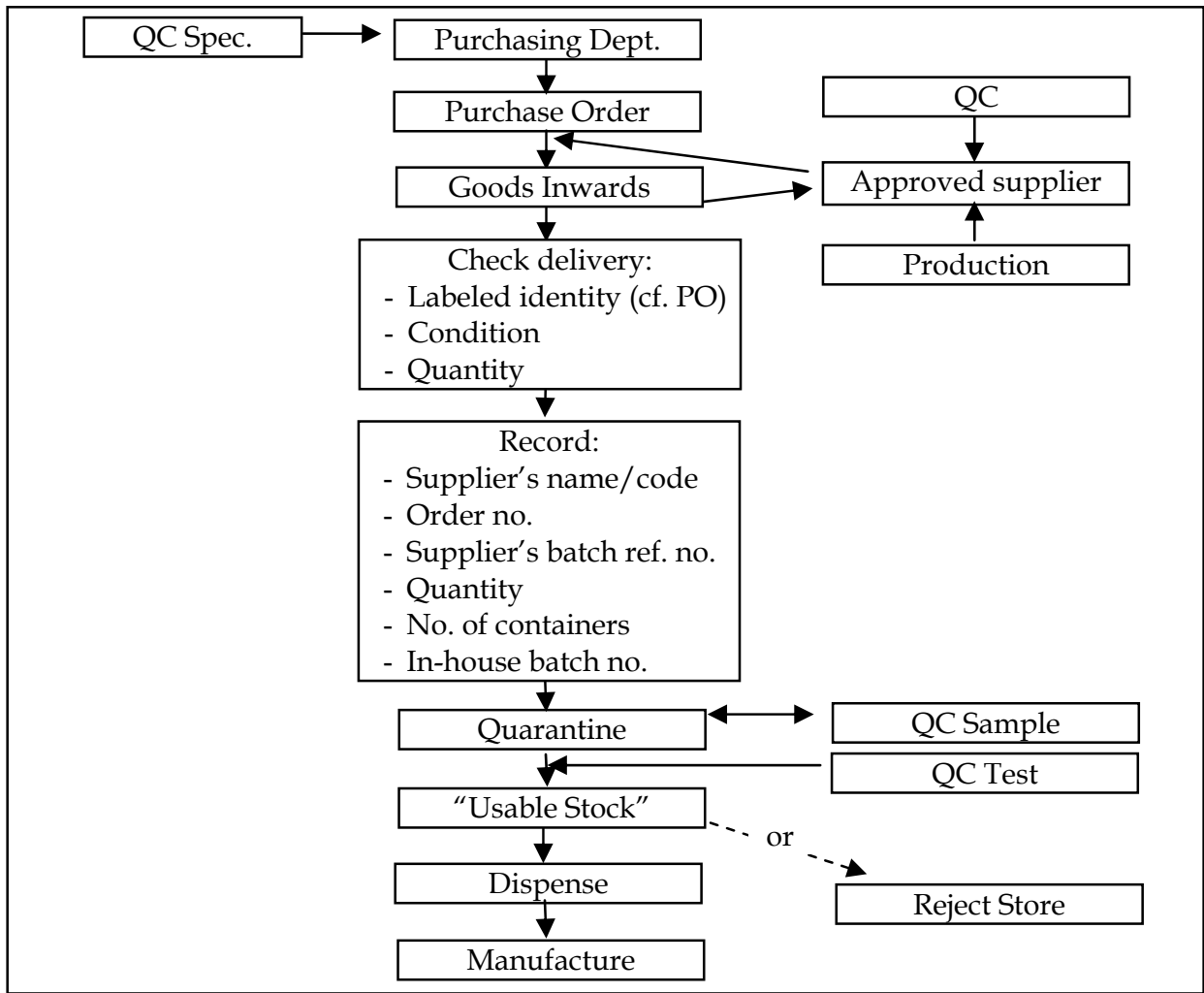


Fig. 13. Components/Starting Materials Flow Chart (Source: Sharp, 2005)

Notes:

- a. It is useful to have the QUARANTINE label, and the RELEASED and REJECTED labels printed in different colors, for example, for QUARANTINE, black print on a yellow background, for RELEASED green print on a white background, and for REJECTED red print on a white background.
- b. In the examples shown, the intention is that, when the QC decision is made, the RELEASED (or REJECTED) label should be applied just over the lower QUARANTINE panel. This may seem an infringement of the golden rule about not applying new labels over old ones, but here (if the, say, RELEASED label falls off, or is removed) the labeled status of the material reverts to QUARANTINE, i.e., it is fail-safe. The benefit of the labeling system illustrated is the elimination of any possible error in transcribing the information originally entered on the QUARANTINE label.
- c. It is important that at least the QUARANTINE label is in a house style, with company name or logo, to avoid confusion with any other identity and status labels (e.g., those applied by vendors) that may already be on the container.

Goods inwards then completes a materials receiving report (Figure 15) in four copies, retaining one copy and sending the other three to QC. They then make the appropriate

ABC Inc.

Code No. Material Lot

Date Rec'd Date Sampled..... By.....

Retest Date

QUARANTINE

Code No. Material Lot

RELEASED

Date QC Sig.

Code No. Material Lot

REJECTED

Date QC Sig.

Fig. 14. Quarantine, Releases and Rejected Labels (Source: Sharp, 2005)

entries (except for entries in the last two columns) in a departmental running record – a “Materials Delivery Record” (Figure 16). This can be a printed sheet or card, or manually drawn up in a record book (or a computer record).

Receipt of the copies of the materials receiving report alerts the QC that the material has been delivered, and is required to be sampled. Following sampling (“date sampled__” and “by__” on the QUARANTINE label completed by the sampler) and testing against the agreed specification, the QC decision is entered on the copies of materials receiving report, one copy being sent to the purchasing department (for information), one to materials inventory control (so, if material is released, it may be allocated to manufacturing batches), and one retained on QC file, with the full analytical report. An authorized member of the QC then places a RELEASED (or REJECTED as appropriate) label, over the QUARANTINE portion, with the necessary details entered. S/he also enters a date at “retest date__” on the original label, to indicate when the material is due for reexamination.

On receipt of the QC decision, goods inwards either moves the released goods into the usable stock area of the stores, or the rejected material to a secure reject store. The two last columns of the material delivery record are then completed (“date approved by QC” and “location”).

GOODS INWARDS - MATERIALS RECEIVING REPORT	
Material..... Code No.	
INSTRUCTIONS: 1. Complete a separate Receiving Report for each delivery, and for each supplier's batch number within a delivery 2. Retain one copy in Goods Inwards file, and send three copies to Quality Control. 3. Quality Control: On completion of testing, mark this report, where indicated. "RELEASED," "REJECTED," "HOLD" as appropriate, and send a copy to: Purchasing Department Materials Inventory Control Retain one copy on Quality Control files	
Date goods received Supplier Supplier's batch no. Quantity received Number of containers Purchase order no. Assigned lot no. General condition/cleanliness of delivery Delivery examined by (signed) Date Remarks/Comments	
QUALITY CONTROL DECISION	

Fig. 15. Goods Inwards -Materials Receiving Report (Source: Sharp, 2000)

Date of Delivery	Material	Code No.	Lot No.	Quantity	No. of Containers	Supplier No.	Delivery Note	Supplier's Batch No. (s)	Supplier's Name for Materials	Date Approved by QC	Location

Fig. 16. Materials Delivery Report (Source: Sharp, 2005)

4.13.1 Packaging materials

The purchase, receipt, sampling, release, and control of printed packaging materials and primary packaging materials (that is packaging materials that come into direct contact with the product, as compared with secondary packaging materials, which do not) need to be accorded the same level of attention as given to starting materials. Documents, records, and procedures analogous to those outlined above should be employed. All the regulatory requirements are in agreement that components or (starting materials) and containers, etc. should be stored and handled in a manner that will prevent contamination. Some

specifically require storage off the floor and suitable spacing “to permit cleaning and inspection.” Some guide adds that one of the objectives of storage “in an orderly fashion” is to “permit batch segregation and stock rotation” [FEFO, “first expiry, first out” or FIFO “first in, first out”]. Storage off the floor guards against damage from flooding and liquid spillages. It also permits wet-cleaning of floors, without the risk of wetting the materials. A well-laid-out, orderly store not only permits segregation of different types, lots, and batches of material (hence, aiding against contamination and mix up) and rotation of stock, it also enables more (labor-, management-, and cost-) efficient running of the store.

4.13.2 Sampling of materials for testing

It is also important that the containers in which the materials are received should be cleaned before the goods are placed in quarantine. A record should be made of all goods received (Materials Delivery Record). The GMP requirements agree that received materials (both components or starting materials and packaging materials) should be held in a quarantined state until they have been sampled, tested for compliance with specification, and formally released for use (or rejected and removed from stock). Quarantine status can be established and maintained by status labeling, by secure physical segregation (for example in separate quarantine store, apart from the usable materials store) or by manual or electronic stock control systems. A combination of all three provides the greatest security against inadvertent use of material that has not been approved for use.

The process of sampling can itself pose risks of contamination. For this reason, containers may need to be cleaned prior to sampling—a vacuum system is very effective for a large container. Small containers may be wiped down with an appropriate solvent or distilled water. Containers should be opened for sampling in an acceptable environment that will not expose the material to further risk of contamination. This sampling area may be a designated room near or adjacent to the warehouse with the provision of reverse laminar flow sampling booth maintaining class 100 condition to avoid cross contamination to or by the material being sampled.

The release of components, containers, and closures for use cannot be for an indefinite time. During storage, degradation may occur, moisture may be absorbed, or materials may simply become contaminated during the storage process. Re-evaluation time scales should be developed from historical data, where possible. Except for particularly sensitive materials, a onetime period, often one year, has been established by many manufacturers. Either the product release label or the system should clearly indicate when materials are to be re-evaluated. This re-evaluation will not usually require full testing, but only examination of those parameters known to be subject to change. For infrequently used materials, re-evaluation coincides with just prior to the use of the material.

4.14 Documentation

Good documentation is an essential part of the QA system and, as such, should exist for all aspects of GMP. Its aims are to define the specifications and procedures for all materials and methods of manufacture and control; to ensure that all personnel concerned with manufacture know what to do and when to do it; to ensure that authorized persons have all the information necessary to decide whether or not to release a batch of a medicine for sale,

to ensure the existence of documented evidence, traceability, and to provide records and an audit trail that will permit investigation. It ensures the availability of the data needed for validation, review and statistical analysis. The design and use of documents depend upon the manufacturer (WHO TRS 961, 2011).

The various types of documents used should be fully defined in the manufacturer's quality management system (QMS). Documentation may exist in a variety of forms, including paper-based, electronic or photographic media. The main objective of the system of documentation utilized must be to establish, control, monitor and record all activities which directly or indirectly impact on all aspects of the quality of medicinal products. The QMS should include sufficient instructional detail to facilitate a common understanding of the requirements, in addition to providing for sufficient recording of the various processes and evaluation of any observations, so that ongoing application of the requirements may be demonstrated (EudraLex, 2012).

There are two primary types of documentation used to manage and record GMP compliance: instructions (directions, requirements) and records/reports. Appropriate good documentation practice should be applied with respect to the type of document. Suitable controls should be implemented to ensure the accuracy, integrity, availability and legibility of documents. Instruction documents should be free from errors and available in writing (EudraLex, 2012).

'If it's not written down, then it didn't happen!' The basic rules in any GMP regulations specify that the pharmaceutical manufacturer must maintain proper documentation and records. Documentation helps to build up a detailed picture of what a manufacturing function has done in the past and what it is doing now and, thus, it provides a basis for planning what it is going to do in the future. Regulatory inspectors, during their inspections of manufacturing sites, often spend much time examining a company's documents and records. Effective documentation enhances the visibility of the quality assurance system. Issue and use of documents should be under formal control. They should be available to all who need them, and *not* available to those who do not. They should be kept up-to-date, but all revisions should be formal and authorized, not haphazard. The documentation system, overall, should be subject to review. It is vital that systems exist for the removal from active use of outdated or superseded documents. (Sharp, 2005)

In the manufacture of anything as important to human health and well-being as medicinal products, every activity must be preplanned and formally defined in advance. Nothing can be left to chance. There is no room for "playing it by ear" or "by the seat of the pants." Manufacture of consistent quality drug products demands consistent, predetermined, *defined* activity.

The objectives are, in short:

1. To state clearly, in advance and in writing, what is to be done
2. To do it – in accordance with those instructions
3. To record what was done and the results of doing it

The reasons for all this documentation are:

1. To ensure there is no doubt about what has to be done, by having formally approved written instructions for each job, and then following them

2. To define standards for materials, equipment, premises, services, and products
3. To confirm, as work proceeds, that each step has been carried out, and carried out *correctly*, using the correct materials and equipment
4. In the longer term, to keep, for later reference, records of what *has* been done, for example, manufacturing and test records, installation, commissioning, servicing, and maintenance records
5. To enable investigation of complaints, defect reports, and any other problems, and to permit observation of any drifts away from defined quality standards
6. To help decide on, and take, any necessary corrective action (including action to prevent reoccurrence) in the event of any complaint or defect report

Document owners are required to ensure that all aspects of documentation and records management specified in form of SOPs. All associates have the responsibility of ensuring that all GMP activities are performed according to the official SOPs; any deviations in procedure are reported to their supervisor and are adequately documented.

There are various types of procedures that a GMP facility can follow. Given below is a list of the most common types of documents, along with a brief description of each.

Site Master File: A document describing the GMP related activities of the manufacturer.

Quality Manual: A global company document that describes, in paragraph form, the regulations and/or parts of the regulations that the company is required to follow.

Policies: Documents that describe in general terms, and not with step-by-step instructions, how specific GMP aspects (such as security, documentation, health, and responsibilities) will be implemented.

Standard Operating Procedures (SOPs): Step-by-step instructions for performing operational tasks or activities.

Batch Records: These documents are typically used and completed by the manufacturing department. Batch records provide step-by-step instructions for production-related tasks and activities, besides including areas on the batch record itself for documenting such tasks.

Test Methods: These documents are typically used and completed by the quality control (QC) department. Test methods provide step-by-step instructions for testing supplies, materials, products, and other production-related tasks and activities, e.g., environmental monitoring of the GMP facility.

Logbooks: Bound collection of forms used to document activities. Typically, logbooks are used for documenting the operation, maintenance, and calibration of a piece of equipment. Logbooks are also used to record critical activities, e.g., monitoring of clean rooms, solution preparation, recording of deviation, change controls and its corrective action assignment.

4.14.1 Hierarchical document system

A company's controlled GMP document system should be established in a hierarchical manner starting with the general regulations and working downward to more specific documents such as batch records (Figure 17).

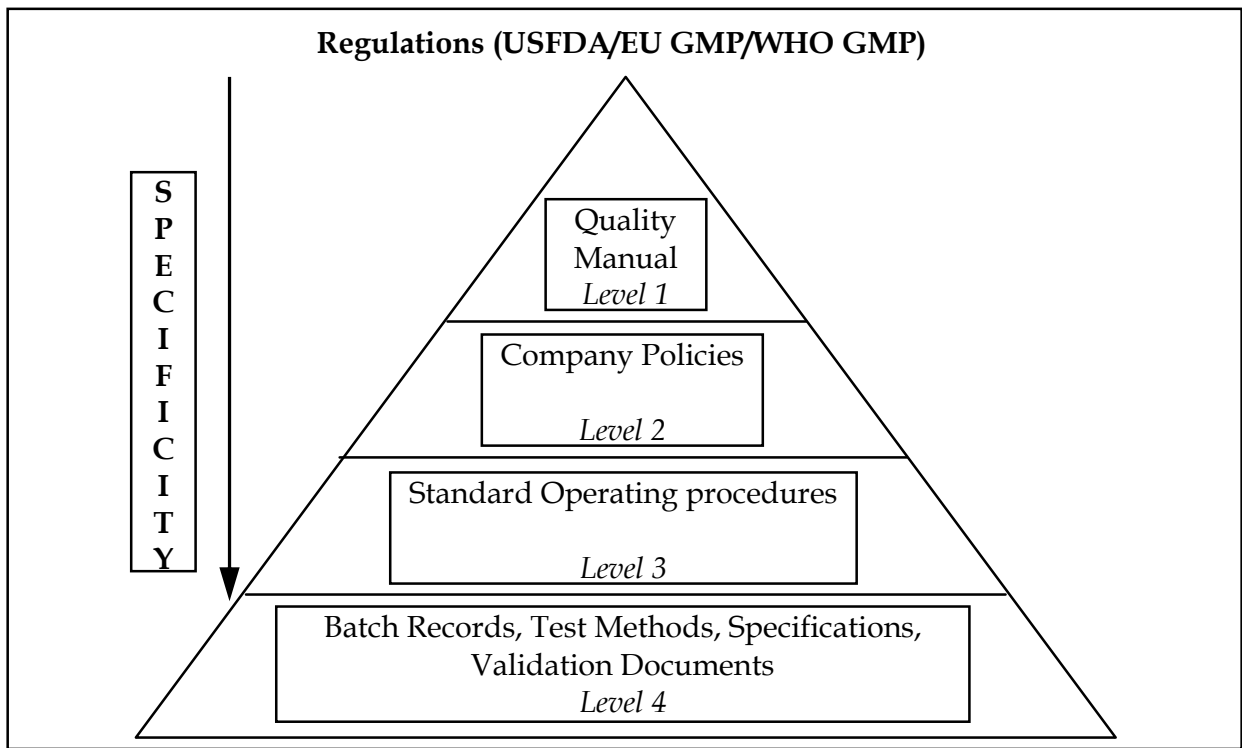


Fig. 17. Document Hierarchical System (Source: Patel & Chotai, 2011)

The regulations that a company is responsible for following (e.g., USFDA/EU GMP/ICH/WHO GMP/Schedule M, etc.) should be at the top of the document pyramid and should govern the directives of the sublevels. The level immediately beneath the regulations, level 1 document (e.g., the Quality Manual), should break the regulations into parts specific to those that the company is required to follow. These documents should establish overall principles and guidelines for how the company plans on developing, documenting, and implementing a GMP-compliant quality system.

The next level, level 2, of documents in the hierarchical document pyramid should further break down the parts of the regulations into specific subjects or topics. These documents (e.g., Company Policies) should establish guidelines with which all subordinate level procedures must comply to ensure consistency across departments. SOPs should be the next level in the document hierarchy after company policy documents. These types of documents should provide specific step-by-step instructions for performing the operational tasks or activities that were talked about in the previous levels. Level 3 documents (i.e., SOPs) should be department specific or function specific. The last level of documents in a document hierarchical structure is level 4 documents. These documents are the most specific in nature, (e.g., batch record, test methods, validation procedures). They apply to a specific department, product, equipment, or process. Level 4 documents provide step-by-step

instructions for production-related tasks and activities as well as provide a means for documenting such tasks using, for example, data sheets, forms, or batch records.

The document hierarchy pyramid is one way of organizing a company's documents. More/less levels may be added/subtracted to meet the company's specific needs. Another way the required GMP documentation may be categorized as;

Instructions (directions, or requirements) type:

Specifications: Documents that list the requirements that a supply, material, or product must meet before being released for use or sale. The QC department will compare their test results to specifications to determine if they pass the test.

Manufacturing Formulae, Processing, Packaging and Testing Instructions: Provide detail all the starting materials, equipment and computerized systems (if any) to be used and specify all processing, packaging, sampling and testing instructions. In process controls and process analytical technologies to be employed should be specified where relevant, together with acceptance criteria.

Procedures: (Otherwise known as Standard Operating Procedures, or SOPs), give directions for performing certain operations.

Protocols: Give instructions for performing and recording certain discreet operations.

Technical Agreements: Are agreed between contract givers and acceptors for outsourced activities.

Record/Report type:

Records: Provide evidence of various actions taken to demonstrate compliance with instructions, e.g. activities, events, investigations, and in the case of manufactured batches a history of each batch of product, including its distribution. Records include the raw data which is used to generate other records. For electronic records regulated users should define which data are to be used as raw data. At least, all data on which quality decisions are based should be defined as raw data

Certificates of Analysis: Provide a summary of testing results on samples of products or materials¹ together with the evaluation for compliance to a stated specification.

Reports: Document the conduct of particular exercises, projects or investigations, together with results, conclusions and recommendations (EudraLex, 2012).

4.14.2 Manufacturing formula and processing instructions

Approved, written Manufacturing Formula and Processing Instructions should exist for each product and batch size to be manufactured.

The Manufacturing Formula should include:

- a. The name of the product, with a product reference code relating to its specification;
- b. A description of the pharmaceutical form, strength of the product and batch size;
- c. A list of all starting materials to be used, with the amount of each, described; mention should be made of any substance that may disappear in the course of processing;

- d. A statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable

The Processing Instructions should include:

- a. A statement of the processing location and the principal equipment to be used;
- b. The methods, or reference to the methods, to be used for preparing the critical equipment (e.g. cleaning, assembling, calibrating, sterilizing);
- c. Checks that the equipment and work station are clear of previous products, documents or materials not required for the planned process, and that equipment is clean and suitable for use;
- d. Detailed stepwise processing instructions [e.g. checks on materials, pre-treatments, sequence for adding materials, critical process parameters (time, temp etc)];
- e. The instructions for any in-process controls with their limits;
- f. Where necessary, the requirements for bulk storage of the products; including the container, labeling and special storage conditions where applicable;
- g. Any special precautions to be observed.

Approved Packaging Instructions for each product, pack size and type should exist. These should include, or have a reference to, the following:

- a. Name of the product; including the batch number of bulk and finished product
- b. Description of its pharmaceutical form, and strength where applicable;
- c. The pack size expressed in terms of the number, weight or volume of the product in the final container;
- d. A complete list of all the packaging materials required, including quantities, sizes and types, with the code or reference number relating to the specifications of each packaging material;
- e. Where appropriate, an example or reproduction of the relevant printed packaging materials, and specimens indicating where to apply batch number references, and shelf life of the product;
- f. Checks that the equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations (line clearance), and that equipment is clean and suitable for use.
- g. Special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before operations begin;
- h. A description of the packaging operation, including any significant subsidiary operations, and equipment to be used;
- i. Details of in-process controls with instructions for sampling and acceptance limits.

4.14.3 Batch processing record

A Batch Processing Record should be kept for each batch processed. It should be based on the relevant parts of the currently approved Manufacturing Formula and Processing Instructions, and should contain the following information:

- a. The name and batch number of the product;
- b. Dates and times of commencement, of significant intermediate stages and of completion of production;

- c. Identification (initials) of the operator(s) who performed each significant step of the process and, where appropriate, the name of any person who checked these operations;
- d. The batch number and/or analytical control number as well as the quantities of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);
- e. Any relevant processing operation or event and major equipment used;
- f. A record of the in-process controls and the initials of the person(s) carrying them out, and the results obtained;
- g. The product yield obtained at different and pertinent stages of manufacture;
- h. Notes on special problems including details, with signed authorisation for any deviation from the Manufacturing Formula and Processing Instructions;
- i. Approval by the person responsible for the processing operations.

4.14.4 Batch packaging record

A Batch Packaging Record should be kept for each batch or part batch processed. It should be based on the relevant parts of the Packaging Instructions. The batch packaging record should contain the following information:

- a. The name and batch number of the product,
- b. The date(s) and times of the packaging operations;
- c. Identification (initials) of the operator(s) who performed each significant step of the process and, where appropriate, the name of any person who checked these operations;
- d. Records of checks for identity and conformity with the packaging instructions, including the results of in-process controls;
- e. Details of the packaging operations carried out, including references to equipment and the packaging lines used;
- f. Whenever possible, samples of printed packaging materials used, including specimens of the batch coding, expiry dating and any additional overprinting;
- g. Notes on any special problems or unusual events including details, with signed authorization for any deviation from the Packaging Instructions;
- h. The quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of obtained product, in order to provide for an adequate reconciliation. Where there are robust electronic controls in place during packaging there may be justification for not including this information
- i. Approval by the person responsible for the packaging operations

4.15 Holding and distribution

It cannot, indeed must not, be considered that concern for the quality of the products of the pharmaceutical industry may cease at the point where the product is filled, sealed, labeled, and approved or released by QC. True QA should extend right up to the point where the product is delivered to the ultimate consumer – the patient. Certainly, there will come a point where the influence that the manufacturer is able to exert will significantly decline. For example, the manufacturer can do little more than advise the dispensing pharmacist on the correct handling and storage of his drug products. Thereafter, the influence of the manufacturer becomes distinctly tenuous. Despite warnings and advice to patients given in

enclosure leaflets, it does seem that many patients neither handle nor take their medicines properly. That said, it is incumbent upon pharmaceutical manufacturers to ensure that having manufactured, packaged and labeled their products, the quality (i.e., “fitness”) of these product remains unimpaired for as far along the supply chain as they are able to exert influence. Manufacturers who distribute via external wholesale dealers should thus ensure that any such wholesale dealer is, indeed, in possession of an authorization to do so.

Whatever their size and type, stores or warehouses all have a few things in common – they receive and take in goods or materials, they hold them (hopefully, safely and securely) for a while, and then they send them out again. Put very simply, even naively, its just a matter of goods in, goods hold, goods out. It may all seem simple, but it is worth pausing to think of how important it really is. Pharmaceutical products can do a lot of good – if they are of the right quality and are used properly. If they are incorrect, damaged, soiled, contaminated, wrongly labeled, have the wrong instructions for use, or have deteriorated, they could fail to have their desired good effects, and could be a danger to the health (or even the life) of the ultimate consumer or patient.

The goods in phase provides an opportunity of checking that purchased materials or bought-in products, or finished products delivered from an internal packaging line, are correct and in good condition. The goods inwards (or receiving) office will normally have a copy of the original purchase order, and the supplying company will usually send with the goods some form of delivery (or advice) note. The order, the delivery note, and the labeling on the goods should all be compared with each other to ensure that everything ties up. At the same time, the delivered goods should be checked for quantity, cleanliness, condition, and for any signs of damage or deterioration. If anything appears to be wrong, it should be reported by the goods-inwards staff immediately, so a decision can be made about accepting the delivery or sending the goods back. There also needs also to be a check on the batch number(s) of the delivery, to see if they match up with the batch numbers on the supplier’s delivery (or advice) note. When a delivery of a particular product or material consists of more than one supplier’s batch number, the different suppliers’ batches should be kept apart from each other, as far as recording, handling, and storing – and any sampling and testing that may be required – are concerned.

It is usual to make a distinction between “returns” and “recalled products.” Returns are products returned from the market to a manufacturer’s warehouse, which are not specifically known to be seriously defective, but which have been sent back by a wholesale or retail customer because of overstocking, superficial damage, or some such similar reason. Recalled products are products that have been withdrawn from the market, at the request of the manufacturer, or the authorities, because of a known or suspected defect.

4.15.1 Goods holding

The goods hold stage is where it is necessary to ensure that the goods remain in good condition, and do not become harmed or damaged through incorrect or unsuitable storage conditions or bad handling. That is, it is important to ensure that quality goods are not reduced to rubbish. All goods must be stored in a clean, neat, orderly way, in conditions that will not affect their quality or cause them to deteriorate in any way. It is not just an issue of looking good. Untidy, scruffy stores are more difficult to run and control. They

increase the possibility of mix-up and confusion — mix-up of different types of goods, mix-up of different batches (or lots), mix-up of goods of different status. It is very difficult to have effective stock rotation unless goods are stored in an orderly fashion.

4.15.2 Goods out — distribution of products

Goods out might well be the last chance of checking and ensuring that everything is in order before the goods leave a manufacturer's hands, to the next step in the distribution chain, on their way to the consumer. It cannot be overstressed that people in stores and warehouses play a vital part in the QA of pharmaceutical products. They must be properly trained and fully aware of the significance of the job they are doing. Particular care is necessary in the picking and assembly of orders for dispatch. It is vitally important to ensure that the items picked are as specified in the customer's order. But it goes further than that. This is perhaps the last chance to check that everything is OK. It is not only important to ensure that the right amounts of the right products, of the right strengths and sizes, are being picked for dispatch. It is also important that a watchful eye is kept open to check that the products being picked are in good condition, that they have been approved for distribution, and that they have not passed their expiry date (or shelf life).

It is necessary to make, and keep, a record of each order that is dispatched, which shows:

- Date of dispatch of goods
- Customer's name and address
- Quantity, name, batch number, and expiry date of each product dispatched

Distribution records must be constructed and procedures established to facilitate recall of defective product. A requisite of the system is approval and specific release of each lot of drug by the QC function before distribution can occur. This control of finished goods for shipment allows only those drugs into commerce that have been shown by testing to conform to appropriate requirements. The manufacturer must maintain records of all distribution transactions involving in process or finished goods. All records should be indexed by either the manufacturing batch lot number or the packaging control number as a means of accountability until the shipment passes from the direct control of the manufacturer. This type of indexing permits an efficient determination of the receiver of a lot to be recalled since only one shipment record need be examined. Depending on the marketing procedures of the individual company, distribution records may list shipments to consignees for packaging or labeling, or to an independent distributor, a wholesaler, a retail pharmacist, a physician, or possibly the ultimate consumer. All distribution records should be maintained for a minimum 3-year period after the distribution process for any control number has been completed. If expiration dating is used for a product, distribution records must be maintained at least for one year past the expiration date of the product.

5. Conclusion

GMP is a production and testing practice that helps to ensure in built quality product. Many countries have legislated that pharmaceutical companies must follow GMP procedures, and have created their own GMP guidelines that correspond with their legislation. Basic

concepts of all of these guidelines remain more or less similar to the ultimate goals of safeguarding the health of the patient as well as producing good quality medicines.

The holder of a manufacturing authorization must manufacture quality medicines so as to ensure the products fit for the intended use, comply with the requirement of marketing authorization and place patients in safe with adequacy, quality and efficacy of the product. Quality objective can be achieved only through careful planning and implementation of QA system and practical implementation of GMP. The effective implementation of GMP requires extensive care and knowledge about the different components of GMP that should be incorporated from the inception of the manufacturing building and product development till the production. *The compliance to QA/GMP does not happen by accident.* The GMP compliance can be achieved as the result of careful planning and installation of quality system. The manufacturers remain responsible for product quality till the shelf life of the product. The effective implementation of GMP requires top level commitment and support from all level of employees of the organization and different external bodies such as government regulatory agencies, material suppliers, distributor, wholesalers, retailers, medical practitioners and the end users of the medicines.

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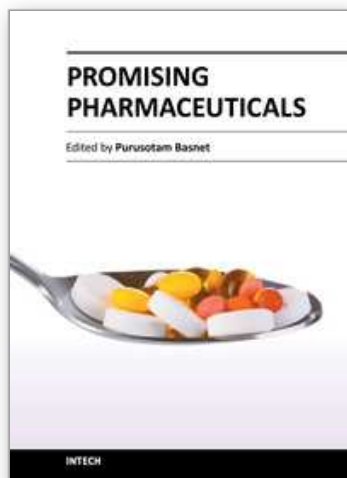
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From the dawn of civilization, humans have been dreaming of happy, healthy and long-life. Our life expectancy is twice longer than 100 years ago. We know more about the diseases. Therefore we have developed new drugs to fight against them. The demand for drugs was so high that we developed Pharma industries. Although Pharma industries took responsibility of producing the needed drugs and gave us a quality of life, misuse of drugs brought further complication. Therefore, discovery, production, distribution, and the phase of administration of patients' quality assurance has to be controlled with a technological procedure and tight regulations to make the system as effective as possible for the benefit of human health. Our book provides selected but vital information on the sources, tools, technologies and regulations regarding the current status of medicine development.

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