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Manufacturing Bulk and Sterile

The in-house preparation of drugs in hospital pharmacy may be categorized into bulk compounding, preparation of nonsterile drugs and sterile manufacturing. The bulk compounding programs is instituted for preparation of drugs not commercially available and modified formulations to be used for clinical or investigation purpose. Whereby sterile manufacturing is used for preparation of sterile topical solution, small volume injectables, special sterile products for clinical and investigational purposes, I/V admixtures and total parenterals in the hospital pharmacy. Under this manufacturing, only those drug dosage forms, strengths, and packaging are prepared which are needed for optimal drug therapy, but which are commercially unavailable.

Most of the pharmacies in Pakistan are not operating a manufacturing program. Some pharmacies are involved in simple compounding. Some major hospitals are involved in preparation of sterile products like total parenterals preparation (TPN), cytotoxic drugs and other I/V admixtures. Manufacturing programs can be further promoted by convincing hospital administrators about the abilities to initiate and manufacturing skills of the hospital pharmacists for this program. If started in an institute, this program offer number of benefits the more important of which are:

1. Development of a close relationship between hospital pharmacist and the physicians.
2. Promotion economy within the hospital.
3. Complementing the operation of formulary system.
4. Making drugs available, which are not commercially available.
5. Enabling physician to cope with the problem of unavailability of the drugs for unusual illnesses.
6. Providing research clinician with the opportunity to develop new pharmaceutical formulations to be use for clinical or experimental purposes.
7. Enhancing the prestige of a hospital pharmacist.

A pharmacist has knowledge of pharmaceutical formulations, formulation problems, stability, sterilization etc. His knowledge and talent can be incorporated in an in-house manufacturing program of an institute.

A pharmacist must note that in-house manufacturing requires the same principles, standards and controls as those employed in the commercial manufacturing. The standards are the models against which a procedure or product is matched and against which the acceptability of the material or procedure are to be judged. The control refers to testing and verification of a procedure and product against certain standards. Control also means to exercise careful restraining power over various manufacturing processes so as these processes can result into a product of required specifications. . The regulations of good manufacturing practice (cGMP) are useful model for developing comprehensive

control systems. A hospital pharmacist incorporates, for the manufacturing program the process, quality and budgetary control.

CONTROL SYSTEMS

MANUFACTURING PROCESS CONTROL

It responsibility of hospital pharmacist to make a product which meet high pharmaceutical standards. Adequate controls over manufacturing eventuate into the products accurate in identity, strength, purity and quality. Sufficient packaging and labeling controls prevent product/package/label mix-ups. Adequate attention must also be given to the stability, palatability, packaging, and labeling requirements of in-house prepared products. A product of high standard can be accomplished by complying with the good manufacturing practice regulations. The good manufacturing practice regulations provide minimum requirements for the preparation of drug product for administration to humans with reference to the premises, environment, men, methods, machinery, documentation etc.

QUALITY CONTROL

Quality of a product is its degree of possession of those characteristics designed and manufactured into it which contribute to performance of an intended function when it is used as directed. Quality control implies procedures by which decision may be made whether a product is meeting standards established previously. This involves the comparison of a process or its output (product) to a standard and evaluating the results of this comparison. Then ultimately, responding, if necessary, with corrective actions that bring the process or its output to within the tolerance. Thus, the quality control is a series of tests, analysis and observations to establish the identity, quality and quantity of a product and to assess its safety, purity and efficacy.

As has been mentioned earlier that materials prepared in hospital pharmacy are expected to have the same degree of quality and safety as any other commercially available pharmaceutical. Quality control is executed to govern quality, purity and strength of the manufactured product.

The quality control in the pharmacy department falls into the following categories:

1. Quality control of raw materials.
2. Quality control of instruments used.
3. Quality control of area to ensure the specified pharmaceutical environment.
4. Quality control of the finished products.

Among various aspects of quality control, the more important is to ensure integrity of label of in-housed prepared formulations. This can best be accomplished by developing a series of cross checks and laboratory analyses.

BUDGETARY CONTROL

The budgetary control is employed to regulate economic aspects of hospital pharmacy manufacturing program. The feasibility of a manufacturing program in hospital pharmacy depends on the budgetary control.

An adequate budgetary control over the manufacturing program, requires careful planning for the manufacturing requirements, raw materials requirement, manufacturing

capacity, available personnel and operating, costs.

Manufacturing Requirements

Determination of manufacturing requirements is a quantitative estimation of manufacturing frequency and the number of particular drugs to be manufactured per annum. The manufacturing requirements can be estimated in terms of rate or production volume, batch quantity, or manufacturing frequency. The manufacturing requirements of any item depend on its expected consumption rate. Prediction accurately of the consumption rate of each item is a difficult task. This can be done however, by reviewing critically records of the previous year and comparing this figure with the staff's present prescribing pattern. Since this practice in not done in country, the manufacturing program will be implemented for the first time. For such an instance, it is suggested to plan for the consumption rate for smaller periods, i.e., consumption rate for one quarter of a year. Such planning will help to modify and correct the manufacturing requirements in case of over or under estimation for the next quarter. Furthermore the drugs are to be prepared in the form of batch. Ideally, the production requirements must not be above the desirable inventory limits.

Material Requirements

Materials for which the planning is done include raw materials, containers, labels, ancillary materials (such as filter paper, filter pads, boxes etc). The estimated manufacturing requirements provide the basis for the prediction of materials requirement for a particular manufacturing program.

The material requirements is accomplished by following two steps:

1. Taking of working formulation formula of each drug to be manufactured and determination of quantity of raw and other materials required to produce the required supply. This is accomplished by taking quantities of raw materials from the working formula and packaging specifications of each item and multiplying these quantities by the number of times the formula must be produced to satisfy the estimated requirement.
2. Preparation of a summary sheet by entering of all required quantities because the same chemical or container may be required by many different formulas. Totaling of quantities under each item on the summary sheet gives estimation of the required supplies and material needed to undertake the intended manufacturing program.

For effective material planning, the required material can be divided into four quarter to allow an ample time to utilize the basic principles of good purchasing technique and at the same time ensures against over inventory and shortage of materials in the pharmacy.

Manufacturing Capacity

The availability of equipments necessary to produce the selected formulas and manufacturing capacity of each equipment are two critical considerations in any bulk compounding program. The type and size of manufacturing equipment required for manufacturing program vary from institution to institution. Primary consideration must be given to scope of manufacturing program, quantities to be produced during any production cycle and as well as to length of time that will be required to consume the product. The availability of personnel and that of the physical facilities are also critical

consideration points.

Modern technology has made possible the availability of equipments that meet every production needs. These are automatic, semi automatic or manual equipments and can handle amounts that are considered to be practical volume/quantity for a particular hospital. The descriptive brochures and catalogues produced by equipment produces assist in selecting the most versatile equipment for a particular use and needs.

For economic reasons, the selection of the equipment should be made on the basis of multiple of uses to which a single piece of equipment can be put. This enables the pharmacist to utilize the equipment at its maximum capacity and prevents costly equipment from accumulating idle time. The selection of such equipments capable to perform variety of functions also prevents space allocation problem may eventuating on having more equipments each performing single operation only.

Manufacturing Staff

Number of manufacturing staff constitutes pharmacist as a supervisor and the ancillary personnel. The number of manufacturing staff is also a very critical factor for economics of a bulk compounding program. Too many personnel will raise cost of manufactured product even more that to purchase it from a commercial supplier. While too little personnel posses inability to maintain an adequate production schedule and potential errors - neither of which may be overlooked.

Reduction in labor cost is the aim of an administrator but under no circumstances should a bulk compounding program be undertaken without services of a pharmacist. The good manufacturing regulations require that a technically competent and qualified pharmacist must supervise manufacturing. However, a pharmacist may be supported with ancillary personnel trained to carry on non-technical tasks such as bottling, filtering, labeling, etc.

Operating Costs

The operating costs include both direct and indirect (overhead) costs. The direct cost is price spent on materials and labor involved in manufacturing. On the other hand, the costs of supervisory personnel, space, equipment depreciation, maintenance, house-keeping, are the indirect or overhead costs. The estimated indirect costs should be compared with the direct costs for the purpose of calculating a ratio of overhead expenses to that of the direct labor expenditures. The true cost of the product can be calculated by using ratio of overhead cost to the direct costs.

Without going into the mathematical explanation, by doubling the quantity of product, doubles the materials costs only and affects little on the overhead expenses. Thus the increase in batch size will, to a point, reduce the unit cost, though this reduction is not geometrically with the increase in batch size. However, manufacture in a volume which will not be consumed within a reasonable period of time poses problems in storage, long term product preservation, and reduced inventory turn-over.

MAINTENANCE OF MANUFACTURING EQUIPMENTS

Maintenance of manufacturing equipments is actually a control over equipment operation. A high investment on pharmaceutical manufacturing equipment and expense associated with frequent repairs necessitate an equipment maintenance program to ensure maximum performance with the lowest possible repair cost. The development of an

equipment maintenance program would be the responsibility of a pharmacist. This can be accomplished by establishing an equipment maintenance record maintained by the pharmacist.

The equipment maintenance record, in addition to identifying equipment as to name, vendor, serial number and cost, also provides a quick history of the repairs employed on it. Furthermore, the routine or preventive monthly maintenance required by the equipment can be recorded and checked off when performed. Omission of the monthly service can be easily detected by reference to this record and corrected prior to the onset of mechanical difficulties.

STERILE MANUFACTURING

The sterile manufacturing involves the same basic principles as required for the bulk compounding only difference of more stringent specifications, sterility and apyrogenicity of the products. Besides various controls discussed earlier, additional environmental controls are needed for sterile manufacturing. components of sterile manufacturing program are intravenous additive program and the intravenous additive services.

INTRAVENOUS ADDITIVE PROGRAM

An intravenous additive program deals with policies and procedures for both, preparation and administration of intravenous fluids to which drugs are to be added. These drugs are incorporated under aseptic conditions. The intravenous additive service on the other hand is a part of the I/V additive program and refers only to the preparation of product. In the I/V additive service, a hospital pharmacist is responsible for:

- Preparation of the final product under aseptic conditions.
- Judicious choice of additive and mixing techniques to avoid interactions.
- Appropriate labeling of final product and properly dispensed or stored.

The availability of such products at odd hours has evolved concept of satellite pharmacy, staffed by a clinical pharmacist and pharmacy technicians. It is obviously essential that these products are to be prepared in an environment conducive to the efficient and safe preparation of them. Usually these solutions are prepared in aseptic environment using laminar flow hoods.

Laminar flow hoods

Laminar airflow is an air movement in which the entire body of air, within a confined area moves with a uniform velocity along parallel flow lines, with a minimum of swirls. A laminar flow hood is a cabinet that provides a constant outward flow of micro-filtered air over entire work area, which clear off the bacteria and dust particles from the ambient atmosphere thus creating an aseptic and sterilized environment in the hood. The laminar flow hoods ensure safe, sterile products production.

Achieving aseptic environment in a bigger room is not possible with less expenditure as compared to get the same in a small cabinet. The laminar flow hoods are commercially available and achieve aseptic environment with economy. These hoods are used for preparation materials requiring sterile techniques. It is also used for handling of sterile research products and preparation of microbiological culture media for such purposes.

A laminar flow hood may be of two types horizontal and vertical (Figure 1) used depending on the nature of the product being prepared.

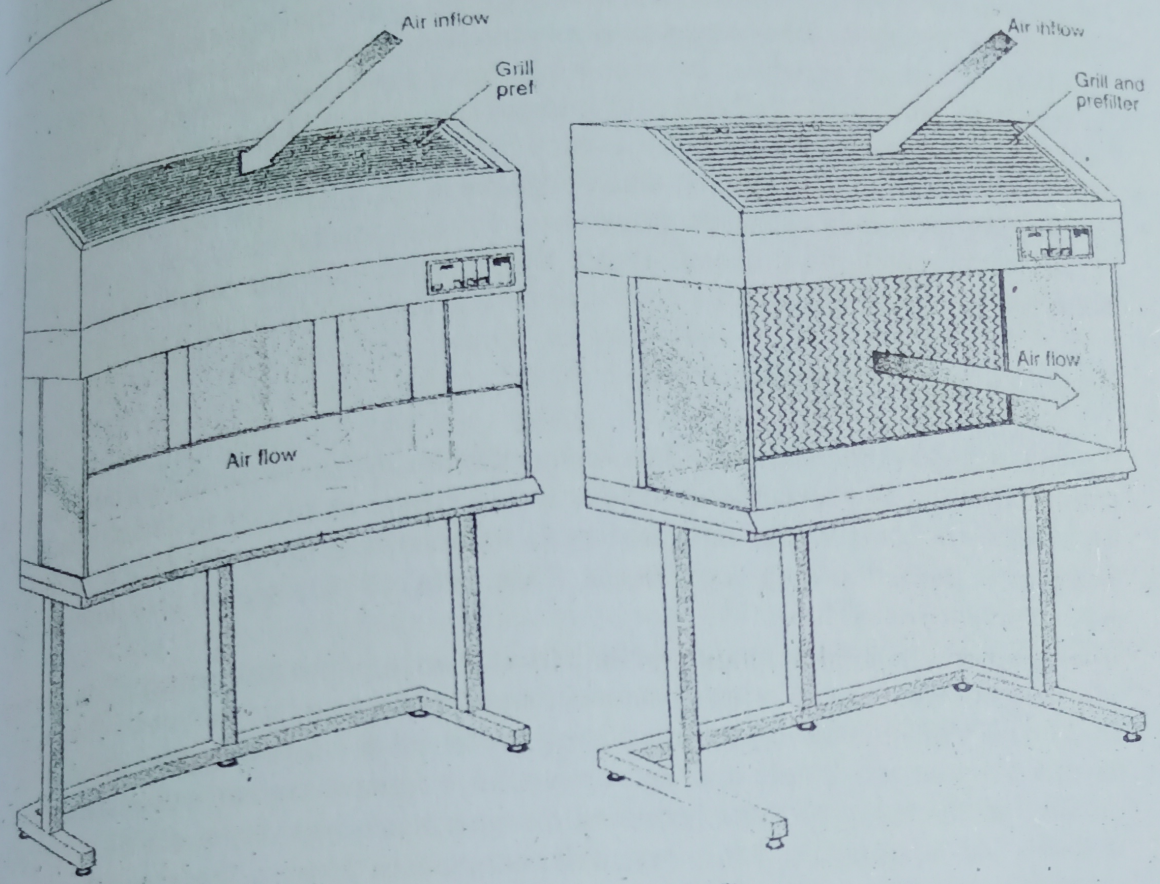

Figure 1: Vertical laminar air flow cabinet and Horizontal laminar air flow cabinet (John Bass Ltd.) From Winfiedl AJ, Richards RME: Pharmaceutical Practice. 2nd Ed. Churchill Liningstone. UK 1990.

Preparation and dispensing of I/V additive solutions

The first step in the preparation of additive solution is the receipt of a physician order. The hospital pharmacist works from physician's order sheet and prepares the label. The label must provide the information as: (a) patient identification with location, (b) physician's name; (c) drugs with quantities added, (d) date of compounding; (e) expiry date, and (f) identification of the pharmacist preparing the product. If the situation demands, an ancillary label should also be prepared at this time. The label is affixed to the container to a position in an upside down in order to facilitate reading when the container is hung from an intravenous solution pole on the patient's bed.

Preparation of I/V solution is carried out under a laminar flow hood using sterile needles and syringes.

Before supplying and giving the preparation to one's another control, the pharmacist must carry out a final inspection of the product. The inspection should include a review of the label, clarity of the solution, and the calculations involved in the preparation.

Areas of knowledge required for preparation of I/V solution

The pharmacist involved in the I/V preparation program should have an understanding of

parenteral feeding therapy, including knowledge of acid-base balance, nitrogen balance, fluid and electrolyte therapy, metabolic and mechanical complications. total parenteral nutrition delivery systems, drug-nutrient and drug-laboratory interactions. Good aseptic technique and experience in preparing intravenous admixtures is essential. The pharmacist should also be aware of current standards and recommendations on sterile admixtures and quality assurance.
For cytotoxic drug admixturing, knowledge areas required have been outlined under the proceeding section on cytotoxic drugs.
Types of preparations prepared under this program are parenteral hyperalimentation solutions and cytotoxic drugs.

Parenteral hyperalimentation

Parenteral hyperalimentation is intravenous administration of sufficient nutrients above the usual basal requirements to achieve tissue synthesis, positive nitrogen balance and anabolism for specific patients unable to tolerate any form of enteral feeding (i.e., nasogastric tube) for long term basis. This form of therapy is also known as total parenteral nutrition (TPN).
The Parenteral hyperalimentation is the part of total care for any patient. The preparation of parenteral hyperalimentation solutions, therefore must an integral part of the pharmacy department's manufacturing program irrespective of its size. The procedures employed for this program are simple and do not require extensive capital outlay for equipment. Because of the nature of these products, the pharmacy must have available appropriate facilities and equipments. Most hospital pharmacists prepare these solutions under a controlled environmental conditions provided by laminar flow hoods. The pharmacist must have knowledge of preparation methods, stability and compatibility, facilities, equipments and environment, required for this program.

Stability and compatibility: The TPN preparation incorporates various ingredients resulting in the production of very complex pharmaceutical systems, particularly where lipid is present. There is much opportunity for interactions and incompatibilities between entities possible, leading to impaired therapeutic value of the preparation or increase risk of its toxicity to patients.
The pharmacists involved in TPN preparations should have a thorough understanding of the potential stability and compatibility issues in these mixtures and be able to advise physicians accordingly and the available literature must be consulted prior to the preparation of TPN.
Facility and environment: As with all aseptic processes, the environment used for manufacturing can contribute considerably to product quality and must thus be designed, cleaned, maintained and monitored to the highest achievable standards. For this purpose, the TPN are prepared in laminar flow hoods as mentioned before.
Personnel and training: Personnel having suitable training should carry out aseptic preparation of TPN solutions. This should cover not only aseptic technique and validation but also theoretical aspects such as patient requirements and use of products.
Documentation: A work sheet should be generated for each TPN dispensing activity for recording materials, patient name, label details, etc. Records pertaining to raw material

testing, environmental monitoring, cleaning, operator training, patients should all form part of the documentation packages which are developed and retained to best fit the requirements of the hospital environment and the standards laid down in Guide to good pharmaceutical manufacturing practice.

Manufacturing procedures: Manufacturing procedures or guidelines should be drawn up jointly by production and quality control staff depending upon the manufacturing environment. All personnel involved in the process, updated regularly and audited periodically should adhere these to ensure conformance. This is essential to the quality assurance of the operation.

The preparation of TNP is initiated on receipt of the request for TPN after the checking of the feasibility and stability within normal clinical limits of requested combination. Information can then be transferred to the dispensing worksheet.

Collection of materials and preparation: The first stage in this process will be the identification and collection together of all materials required to be taken into the aseptic suite. The components assembled are then checked against the work sheet by the pharmacist who should initial the sheet. At this stage either the work sheet or label containing a copy of the formulation should be passed through with the ingredients, utilizing a transparent pocket which can be swabbed.

Formulation: Where more than one TPNs are being processed in the preparation room, care should be taken to avoid intermixes of source materials, labels, etc. and another reconciliation should be carried out prior to the passage of materials into the aseptic cabinet or room.

As with all aseptic operations, materials should be placed well within the laminar air flow cabinet making use of all the available space and organized in a manner which will facilitate the pre-defined systematic steps in the dispensing process and cause minimum disruption of air flow.

Inspection: The completed nutrition bag should be inspected to check for integrity of all ports, leaks, splits and particulate, for which TPN solutions should conform to compendial criteria together with the limit test for particulate matter.

Labeling: In general the following information will be required on the label:

1. Patient name/number
2. Ward
3. Product constituents
4. Batch (dispensing number)
5. Expiry date/time
6. Storage conditions
7. Other instructions such as guidance on administration rate or technique, limitations on further additions etc., may also be required.

Storage: The compounded TPN solutions should recommended to be stored at 2 - 6°C to protect it from microbiological and chemical degradation factors. The bags containing lipid, should not be allowed to freeze and should not be stored at room temperature for periods in excess of the 12 - 24 hours required for administration.

Packaging: Where supplies of compounded product are to be made to hospitals patients away from the site of manufacture, the quality of the packaging system must be validated comply with quality control standards and to maintain product temperature during transit. Insulated polystyrene containers may be usefui for this purpose.

Dispensing: The TPNs are dispensed according to procedure mentioned above. The hospital pharmacist may be involved in development of nursing care guidelines with particular reference to further additions, storage, etc. It may also be useful for the ward pharmacist to check that TPN is being correctly administered.

Charging of TPN: A TPN compounding service within a hospital is a costly venture for the pharmacy department. Amino acid and lipid presentations are, by their special nature, expensive items to purchase. Pricing of the prepared TPN requires the identification of the compounding materials cost and other, sometimes not so apparent, costs such as labor input, overheads, consumables. etc.

All these factors must be considered when developing true service costs and deciding whether to produce in-house or obtain product from a another hospital or commercial source.

Cytotoxic agents

The cytotoxic drugs are capable of killing cells and thus are employed in the treatment of cancer and to destroy tumor and neoplastic cells. Most of the injectable cytotoxics are powdered preparations that need reconstituting before use.

The pharmacists can provide a cytotoxic reconstitution service. They have extensive knowledge in areas of pharmaceutics, pharmacology, pharmaceutical chemistry and pharmacokinetics that are basic to the understanding of the action of cytotoxics in the body and their stability in solution. Pharmacists and technicians should be well trained in aseptic technique, recording and checking procedures to ensure that the patient receives an appropriate dose of the correct drug that often has a small therapeutic range. The pharmacist can utilize his pharmaceutical knowledge to provide a safe and efficient service for the dispensing of cytotoxic drugs.

Areas of skill needed for pharmacist

The knowledge of the following aspects is essential for a pharmacist undertaking cytotoxics program in hospital pharmacy:

Safe handling: So far these agents have been nonselective and destroy some healthy tissue as well thus, personnel handling the drugs may be at risk if sensible precautions are not taken.

The uncontrolled exposure of cytotoxics of personnel may lead to irritant to mucous membranes, eyes and skin, lightheadedness, djzziness, nausea, headache and allergic reactions. The risks of malignancies, leukaemias, teratogenesis and infertility may also increase if a worker with unsafe practice due to exposure for a longer period of time.

Measurable exposure may be minimized by instituting safe handling practices. If procedures are followed, areas of possible direct exposure such as skin contact, inhalation of aerosolized drug or ingestion can be eliminated.

Preparation areas: Use of laminar air flow cytotoxic cabinet provides product protection by allowing contamination free air as well as worker's protection achieved by venting away of cytotoxic contamination outside. The cytotoxic cabinet should be reserved solely for preparation of cytotoxic agents.

The ventilation of the area should be adequate, but doors and windows should be closed to exclude draughts. The working surface should be non-porous to substances being

handled and be easily cleaned. The equipment and stocks of cytotoxic drugs should be arranged in a safe and orderly manner to avoid accidents.
Neutralizing solutions to cope with spills should also be close to hand. Horizontal laminar flow cabinets should never be used to reconstitute cytotoxics as particles and aerosols could be blown towards the operator.
Techniques and precautions: Prior to dispense an intravenous cytotoxic agent is to be reconstituted whilst maintaining sterility of the product and also ensuring the maximum degree of safety to the operator. Prohibiting eating, smoking, drinking and application of cosmetics in the work area prevent ingestion. Wearing of suitable protective clothing and gloves protects skin contact. Gloves made of latex should be worn unless directed otherwise by specific instructions from the manufacturer.
Surgical face-masks will not completely prevent inhalation of aerosols but they may help. Goggles to protect the eyes should be worn and should be washed in water after use.
Reconstitution should be carried out on a solid surface that can be cleaned easily. A broad-edged tray may be suitable if a vertical laminar air flow cabinet lacks a continuous solid surface (i.e. the working area is perforated). Plastic-backed paper may also be used as a work surface as long as it does not compromise a stable working surface,
Prevention of aerosol formation from cytotoxic vials: Aerosolization occurs due to the pressure differentials between the inside and outside of a vial. Aerosolization of cytotoxic agents should always be prevented and is achieved by equalizing pressure between syringe and vial. The replacing of the volume of fluid drawn out of the vial with an equal volume of air from the syringe equalizes the pressure. Always ensure, however, that negative pressure is maintained within the vial. A volume of air or fluid should never be pushed directly into the vial but added in small volumes, allowing equalization of pressure. An alternative method is to vent the vial using a needle connected to a hydrophobic filter. This allows air in and out of the vial but prevents fluid and particles being expelled.
Aerosols may also be produced when opening ampules. To prevent this, any material in the top of the ampule should be tapped down gently.
If air bubbles have to be expelled from the syringe these may be vented back into the container
Coping with spills and waste disposal: Detailed procedures for coping with spills and waste disposal must be distributed to all staff handling cytotoxic agents, detailing action to be taken if spillage should occur. A general procedure should be available to ensure prompt first-line action. A manufacturing pharmacist must know all the protective measures and instruments.
Disposal: Equipments used to prepare cytotoxics, intravenous administration sets, and other contaminated materials should be placed in high-risk waste-disposal bags. Disposal of sharp objects, e.g. syringes and needles, empty vials and ampules, should be placed in suitable rigid containers and labeled with a hazard warning seal.