

# **Preface**

**Praise be to Allah and Peace be upon His Prophet Mohammed –  
the Most honourable of His Messengers.**

The mission of the Executive Board, Council of Health Ministers for GCC States is to obtain safe and effective drugs to be provided to the consumer at high quality and specifications. This is, too, one of the objectives of central drug registration in the Executive Board.

Having realized that Good Manufacturing Practice (GMP) is an important element in obtaining safe and effective drugs, The Health Ministers' Council for the GCC States has given this subject a great attention.

Many ministerial resolutions have been issued which affirmed the importance of implementing the principle of GMP, whether at local or international factories. On the other hand, emphasis was made on visiting the companies submitting for registration to make sure they are applying the GMP as required.

In the same line, it was found necessary to have guidelines prepared by the E.B. Therefore, the Gulf Committee for Central Drug Registration, prepared a manual for GMP, which is considered a right step towards performance quality guided by specific criteria and specifications.

I hope that this manual will be of great use to all interested people especially pharmacists who undertake the responsibility of visiting factories so as to submit high quality and valid reports. I ask the Almighty Allah to keep us and your goodselves

away from any assaults, and help us realize the prosperity and flourishing we look forward to in the context of the care and follow up of Their Excellencies the Health Ministers in the member states, and the great care of our patrons – Allah bless them all.

**Dr Tawfik A. M. Khoja**  
**Director General**

## **GENERAL GCC GUIDELINES For Good Manufacturing Practice For Various Types of Medicinal Products**

The objectives of The Executive Board of The Health Ministers' Council for the GCC States are to control and enforce general standards of production and to provide authorization for the manufacturer to produce specific pharmaceutical products to be marketed within the gulf region.

Inspection of local and overseas manufacturers is essential, and guidelines are produced to describe the aims and the procedure to be carried out during an inspection visit.

The registration of any new pharmaceutical product, or a new manufacturing company, will not be commenced before ensuring that the manufacturing company is complying with all the cGMP rules and regulations set by WHO and other recognized international standards(MCA's Rules and Guidance For Pharmaceutical Manufacturers and Distributors 1997).

Therefore, periodical inspection of the manufacturing company is necessary to ensure an up-to-date good manufacturing conditions/operations in all local and foreign manufacturers.

### **Qualification(s) and Role(s) of the Inspectors:**

- Inspectors should have a Bachelor degree in Pharmacy with a practical experience and training in cGMP.
- NEW inspectors with limited experience should accompany experienced inspectors on site visits as well as participating in courses and seminars on cGMP relevant topics.

- The primary role of an inspector is to present a detailed factual report on standards of manufacture and control applied to specific products and does not breach understanding regarding confidentiality of information having commercial value.
- An inspector should keep a positive manner by providing advice on how production and control procedures can be usefully upgraded or by offering ideas based on the cGMP rules which might serve the public interest and not just compiling a list of faults, irregularities, and discrepancies.

### **The Inspection Process:**

The precise objective of the inspection determines the nature of the inspection process and the resultant report generated after it.

There are 3 types of processes to be carried out depending upon the objective of the inspection:

#### **1. Routine inspection:**

A full and precise inspection to ensure all the cGMP requirements have been fulfilled. This type is applied to the following::

- If the manufacturer is newly established.
- “ “ “ requests a license renewal to operate.
- If the manufacturer has introduced a new production line.
- If the manufacturer has introduced a new product according to justification.
- If the manufacturer has made significant changes in the manufacturing process, key personnel, premises, equipment, ...etc.
- If the manufacturer has a history of noncompliance with GMP and did not pass previous inspection process.

#### **2. Concise inspection:**

This is carried out on manufacturers with a consistent record of compliance with the cGMP requirements through previous inspections.

Concise inspection focuses on limited numbers of GMP requirements, in addition to observing any significant changes that could have been introduced since the last inspection.

Concise inspection provides the inspector with an overall attitude of the firm towards cGMP, and whether it may or may not trigger a more comprehensive inspection.

**3. Follow-up inspection (re-assessment or re-inspection):**

Follow-up visits are made to monitor the results of the corrective actions which are normally carried out 6 months after the initial inspection depending on the nature of the defects.

**The Inspection Team:**

The inspection team should consist of not less than 3 inspectors. The chairman of the team is the person who has the most experience, skills, and best knowledge in this particular field of work.

It is recommended that two of the team members should have good experience in this particular field [ while the third member can be a trainee] in case the chairman fails to attend the inspection whether before traveling or during the inspection due to any circumstances.

**Frequency and Duration of the Inspection**

**Process:**

The schedule and duration of the actual inspection process should be pre-decided among the manufacturer and the Executive Board of Health Ministers' Council.

**Steps of the Inspection Visit:**

1. A meeting is held between the inspectors and the company representatives. The plant manager ( or his/her representative) provides an overview of the company's activities, products, and a description of the production process involved.
2. The Product flow: The inspection usually starts at the warehouse (but not necessarily), then the production area, and finally the quality control area.
3. Observations are precisely recorded by the inspectors.

4. A short checklist can be used to ensure that all areas have been investigated.
5. A final briefing is held between the inspectors and the company representatives after the completion of the inspection process where the inspectors list any unsatisfactory findings and irregularities or other observations to be covered for the attention of the management team in a positive manner.
6. Photographs and videos may be taken during the visit.
7. The inspection team should prepare the final report which is submitted and presented, signed and dated by each of the inspectors, to the Executive Board of The Health Ministers' Council for the GCC States which is then forwarded to the GCC Central Registration Committee to be discussed in following meeting.

### **The Inspection Report:**

The final report should consist of **4 parts:**

**a. Part I:**

Consists of general information about the company in addition to a summary of the inspection process involved and the objectives of the visit. General impression of the company and any complaint reports about the products and/or the manufacturing process during the last 2 years must be presented.

The inspection date and the name of the inspectors must be included.

If in any case a member of the inspection team fails to attend the inspection visit, the reason should be mentioned.

**b. Part II:**

This is a simple description of the inspection process involving the production line being inspected and the product in concern, including the samples taken during the inspection process.

**c. Part III:**

Inspectors should record any Negative Observations: i.e. all the faults, defects, irregularities and discrepancies in details.

***d. Part IV:***

The last part of the inspection process should cover the inspectors' suggestions and whether the company is complying with GMP or not.

Each member of the inspection team must sign the final report, and if possible, attach any additional document to report such as a list of the products manufactured by the company, the annual company report, photographs, video's...etc

***GCC-DR actions upon companies' visits***

**The following procedure should be undertaken:**

- A. The inspection team prepares the final report that outlines the observations made during the inspection process. The recommendations, suggestions, or any other ideas made by the team to assist the manufacturer in complying with the cGMP requirements and any modifications made on any specific deficiencies should be mentioned.
- B. The report is submitted to Central registration section to be discussed in the next meeting. In all cases, a copy of the final report should be received by the members of the GCC states before the meeting.
- C. The committee decides on the status of the company in the following meeting.
- D. The central registration committee contacts the regulatory authorities in the member states about the decision of the Committee.
- E. There are 2 **conditions**:
  - I. full approval once the company fulfilled the cGMP requirements and the member states are informed accordingly.
  - II. if the inspection team has reported some observations about noncompliance, the head of the central registration section should follow-up with the manufacturer. If the manufacturer responds positively, the head of the GCC central registration should convey the report to the members of the inspection team. If the inspection team has approved the amendments, the final report should be submitted to all member states to be discussed in the following meeting. If the inspection team has not agreed on the amendments and they may request a second visit, the head of the central registration section should raise the matter in the following committee meeting for their decision which should be conveyed to the manufacturer. The whole process should not take more than 6 months.

- F. After the above process and the failure to comply with cGMP, then the issue of the registration will not be considered before the elapse of 2 years.
- G. If the company fulfills the cGMP requirements and the GCC Central Registration **Committee approves it, a GMP certificate will be generated to the intended company.**

The company now is eligible for Central Registration in the GCC member states.

**Guidelines for the manufacture of the following products will be discussed:**

1. Sterile Medicinal Products
2. Biological Medicinal Products
3. Medicinal Products Derived From Human Blood or Human Blood.
4. Liquids, Creams and Ointments.



## **1- MANUFACTURE OF STERILE MEDICINAL PRODUCTS**

### **Principle:**

1. Sterile medicinal products are subject to special requirements in order to minimize risks of microbial contamination, and of particulate and Pyrogen contamination.
2. Manufacture of sterile medicinal products requires skilled, well-trained, highly experienced and well-qualified personnel.

### **General Guide:**

1. The manufacture of sterile products should be carried out in clean areas, entry to which should be through airlocks for personnel and/or for equipment and materials.
2. Clean areas must be maintained to appropriate cleanliness standard and supplied with air, which has passed through filters of an appropriate efficiency.
3. Each manufacturing operation requires an appropriate environmental cleanliness level in the operational state in order to minimize the risks of particulate or microbial contamination of the product or materials being handled.
4. Four grades can be distinguished for the manufacture of sterile medicinal products:
  - A. Grade A: Local zone for high risk operations both in the “at-rest” and “at-operation” states normally supplied with laminar air flow work station which provides a homogenous air speed of 0.45m/s +/- 20%(guideline value) at the working station.
  - B. Grade B: In the “at-rest” state, i.e. in case of aseptic preparation and filling, it is the same as Grade A zone.
  - C. Grade C & D: These are clean areas for carrying out less critical stages in the manufacture of sterile products.

**The airborne particulate classification for these grades is given in the following table:**

Grade	At rest		In operation	
	Maximum permitted no. of particles/m <sup>3</sup> equal to or above			
	0.5µm	5µm	0.5µm	5µm
A	3 500	0	3 500	0
B	3 500	0	350 000	2000
C	350 000	2000	3 500 000	20 000
D	3 500 000	20 000	Not defined	Not defined

**Examples of operations to be carried out in various grades are given in the following table:**

Grade	Example of operations for terminally sterilized products.
A	Filling of products, when unusually at risk.
C	Preparation of solutions, when unusually at risk. Filling of products.
D	Preparation of solutions and components for subsequent filling.
Grade	Examples of operations for aseptic preparations
A	Aseptic preparation and filling
C	Preparation of solution to be filtered
D	Handling of components after washing

5. In order to control the particulate and microbiological cleanliness of the various grades in operation, the areas should be monitored. Sampling methods should not interfere with zone protection. Results from monitoring should be considered when review batch documentation for finished product release.
6. Surfaces and personnel should be monitored after critical operations.
7. Additional microbial monitoring is also required outside the production operations e.g. after validation of systems, cleaning and sanitization.

**Recommended Limits for microbial monitoring of clean areas in operation:**

<b>Recommended limits for microbial contamination</b>				
<b>Grade</b>	<b>Air sample (cfu/m<sup>3</sup>)</b>	<b>Settle plates (diam.90mm), cfu/4hours</b>	<b>Contact plates (diam.55mm), cfu/plate</b>	<b>Glove print 5 fingers cfu/glove</b>
A	<1	<1	<1	<1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

8. Appropriate alert and action limits should be set for the results of particulate and microbiological monitoring. If limits are exceeded, operating procedures should prescribe corrective actions.

**Terminally Sterilized Products:**

9. Grade D or more: preparation of components and most products is done here to give low risk of microbial and particulate contamination, suitable for filtration and sterilization.

Grade C or more: Preparations are carried out in areas where there is unusual risk to the product because of microbial contamination e.g. because the product actively supports microbial growth or there must be help for a long period before sterilization, or is necessarily processed mainly in closed vessels. Operations to be carried out include filling of the products for terminal sterilization, preparation of ointments, suspensions, creams and emulsions before sterilization.

Grade A with at least a grade C Background: here the product is at unusual risk of contamination from the environment e.g. the filling operation is slow

or the containers are wide-necked or are necessarily exposed for more than few seconds before sealing.

### **Aseptic Preparations:**

10. Grade D or more: Components handling after washing.

Grade C: preparation of solutions which are to be sterile filtered during the process.

Grade A with grade B Background: if not to be sterile filtered, the preparation of materials and products should be done in this environment. Also handling and filling of aseptically prepared products.

Preparation and filling of sterile ointments, creams, suspensions and emulsions when the product is exposed and is not subsequently filtered.

Grade B: Transfer of partially closed containers in sealed transfer trays.

### **Personnel:**

11. The following conditions apply to the **personnel**:

- Only the minimum number of personnel required should be present in clean areas, particularly during aseptic processing.
- All personnel (including those concerned with cleaning and maintenance) employed in such areas should receive regular training and disciplines relevant to the correct manufacture of sterile products.
- When outside staff need to be brought in, particular care should be taken over their instruction and supervision.
- Staff engaged in the processing of animal tissue materials or of cultures of microorganisms should not enter sterile product areas unless rigorous and clearly defined entry procedures have been followed.
- Periodic health checks are desirable.
- Any condition which might cause shedding of abnormal numbers of contaminants should be reported.
- Changing and washing should follow a written procedure designed to minimize contamination of clean area clothing or carry-through of contaminants to clean areas.
- Wrist watches, make-up, and jewelry should not be worn in clean areas.

- The clothing and its quality should be appropriate for the process and grade of working area. It should be worn in such a way as to protect the product from contamination.
- For any worker in grade A/B area, clean sterile protective garments should be provided at each work session. Gloves should be regularly disinfected during operations.
- Masks and gloves should be changed at least at every working session.
- Separate cleaning and handling facilities PLUS standard operating procedures are desirable.

**Premises:**

12. The following standards apply to the **premises:**
- In clean areas, all exposed surfaces should be smooth, impervious and unbroken in order to minimize the shedding or accumulation of particles or microorganisms and to permit the repeated application of cleaning agents and disinfectants where used.
  - To reduce accumulation of dusts and to facilitate cleaning, there should be no uncleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment. Sliding doors are undesirable for that reason.
  - Sinks and drains should be prohibited in grade A/B areas used for aseptic manufacture.
  - Floor drains in lower grade clean rooms should be fitted with traps or water seals to prevent back flow.
  - Changing rooms should be designed as airlocks and used to provide physical separation of the different stages of changing. They should be flushed effectively with filtered air.
  - The final stage of the changing room should be the same grade as the area into which it leads.
  - Hand washing facilities should be provided only in the first stage of the changing rooms.

- Both airlock doors should not be opened simultaneously. An interlocking system or visual and/or audible warning system should be operated to prevent the opening of more than one door at a time.
- Decontamination of facilities and treatment of air leaving a clean area may be necessary for some operations.
- Air-flow patterns must not present any contamination risk e.g. air flow should not distribute particles from a particle-generating person, operation of machine to a zone of higher product risk.
- A warning system should be provided to indicate failure in the air supply.

### **Equipment:**

13. The following standards apply to the **equipment**:

- A conveyor belt should not pass through a partition between grade A or B area and a processing area of lower air cleanliness, unless the belt itself is continually sterilized (e.g. in a sterilizing tunnel).
- As far as possible equipment, fittings and services should be designed and installed so that operations, maintenance and repairs can be carried out outside the clean area. If sterilization is required, it should be carried out, wherever possible, after complete reassembly.
- When equipment maintenance has been carried out within the clean area, the area should be cleaned, disinfected and/or sterilized where appropriate, before processing recommences if the required standards of cleanliness and/or asepsis have not been maintained during the work. Check if maintenance has been logged, e.g. laminar flow station certification and what cleaning, etc has been logged and monitored before commencement.
- Clean area should be cleaned, disinfected and/or sterilized where appropriate, before processing recommences particularly when the equipment maintenance has been carried out within the clean area.
- Water treatment plants and distribution systems should be designed, constructed and maintained so as to ensure a reliable source of water of an appropriate quality. They should not be operated beyond their designed capacity. Water for injections should be produced, stored and

distributed in a manner which prevents microbial growth, for example by constant circulation at a temperature above 70°C

- All equipment such as sterilizers, air handling and filtration systems, air vent and gas filters, water treatment, generation, storage and distribution systems should be subject to validation and planned maintenance, their return to use should be approved.
- It should be demonstrated that airflow patterns do not present a contamination risk, for example care should be taken to ensure that airflows do not distribute particles from a particle-generating person, operation, or machine to a zone of higher product risk.

### **Sanitation:**

14. The following standards apply to the sanitation **systems:**

- Clean areas should be cleaned thoroughly in accordance with a written program.
- Monitoring should be undertaken regularly to detect the development of resistant strains.
- Disinfectants and detergents should be monitored for microbial contamination.
- Disinfectants and detergents used in Grade A and B areas should be sterile prior to use.
- Fumigation of clean areas maybe useful for reducing microbiological contamination in inaccessible places.
- Where disinfectants are used, more than one type of disinfectant should be used with periodic alteration.

### **Processing:**

15. The following conditions apply to processing of sterile medicinal **products:**

- Precautions to minimize contamination should be taken during all processing stages including the stages before sterilization.
- Preparations of microbiological origin should not be made or filtered in areas used for the processing of other medicinal products; however, vaccines of dead organisms or of bacterial extracts maybe filled, after

inactivation, in the same premises as other sterile medicinal products. Check blood handling procedures.

- The form of the nutrient medium used above should generally be equivalent to the dosage form of the product.
- The process simulation test should imitate, as closely as possible, the routine aseptic manufacturing process and include all the critical subsequent manufacturing steps.
- Process simulation should be repeated at defined intervals and after any significant modification to the equipment and process. The number of containers used for a medium fill should be sufficient to enable a valid evaluation. For small batches, the number of containers for the medium fill should be at least equal the size of the product batch. The contamination rate should be less than 0.1% with 95% confidence level. Check incubation temperatures for ATTACK and justification.
- Care should be taken that any validation does not compromise the processes.
- Water sources, water treatment equipment and treated water should be monitored regularly for chemical and biological contamination and, as appropriate, for endotoxins. Records should be maintained of the results of the monitoring and of any action taken.
- Activities in clean areas and especially when aseptic operations are in progress should be kept to a minimum and movements of personnel should be controlled and methodical, avoid excessive shedding of particles and organisms due to over-vigorous activity. The ambient temperature and humidity should not be uncomfortably high because of the nature of the garments worn.
- Records of the results of monitoring and of any action taken; should be maintained.
- Microbiological contamination of starting materials should be minimal, specifications should include requirements for microbiological quality by monitoring.
- The interval between the washing and drying and the sterilization of components, containers and equipment as well as between their sterilization and use should be minimized and subject to a time-limit appropriate to the storage conditions.



- There should be working limits on contamination immediately before sterilization which are related to the efficiency of the method to be used.
- Where appropriate, the absence of pyrogens should be monitored specially for water.
- Components, containers, equipment and any other article required in a clean area where aseptic work takes place should be sterilized and passed into an area through double-ended sterilizers sealed into the wall, or by any procedure which achieves the objective of not introducing contamination.
- The efficiency of any new procedure should be validated.
- Validation should be verified at scheduled intervals based on performance history or when any significant change is made in the process or equipment.

### **Sterilization:**

16. The following points apply:

- All sterilization processes must be validated, particularly when the adopted sterilization method is not described in the current edition of European Pharmacopoeia or other national standards, or when it is used for a product which is not a simple aqueous or oily solution. Where possible, heat sterilization is the method of choice. In any case, the sterilization process must be in accordance with the marketing and manufacturing authorizations.
- Sterilization can be achieved by moist or dry heat, by ethylene oxide (or other suitable gaseous sterilizing agent), by filtration with subsequent aseptic filling of sterile final containers, or by irradiation with ionizing radiation (but not with ultraviolet radiation unless the process is thoroughly validated). Each method has its particular applications and limitations. Where possible and practicable, heat sterilization is the method of choice.
- Suitability and efficacy in achieving the desired sterilizing conditions in all parts of each type of load to be processed should be demonstrated. This work should be repeated at scheduled intervals, at least annually,

and whenever significant modifications have been made to the equipment.

- Records of the results should be kept.
- Biological indicators should be considered only as an additional method for monitoring the sterilization. They should be stored and used according to the manufacturers instructions, and their quality checked by positive controls. If they are used, strict precautions should be taken to avoid transferring microbial contamination from them.
- For effective sterilization, the whole of the material must be subjected to the required treatment and the process should be designed to ensure that this is achieved.
- There should be a clear means of differentiating products which have not been sterilized from those which have. Each basket, tray or other carrier of products or components should be clearly labeled with indication of whether or not it has been sterilized. Indicators such as autoclave tape may be used, where appropriate, to indicate whether or not a batch (or a sub-batch) has passed through a sterilization process, but they do not give a reliable indication that the lot is, in fact, sterile.
- Sterilization records should be available for sterilization run. They should be approved as part of the batch release procedure.

### **Sterilization By Heat:**

- Each heat sterilization cycle should be recorded on a time/temperature chart with a sufficiently large scale or by other appropriate equipment with suitable accuracy and precision. The temperature should be recorded from a probe at the coolest part of the load or loaded chamber, this point having been determined during the validation; the temperature should preferably be checked against a second independent temperature probe located at the same position. The chart, or a photocopy of it, should form part of the batch record. Chemical or biological indicators may also be used but should not take the place of physical controls.
- Sufficient time must be allowed for the whole of the load to reach the required temperature before measurement of the commencement of the sterilizing time-period. This time must be determined for each type of load to be processed.

- After the high temperature phase of a heat sterilization cycle, precautions should be taken against contamination of a sterilized load during cooling. Any cooling fluid or gas in contact would not be approved for use.

### **Moist Heat:**

- Sterilization by moist heat is suitable only for water-wettable materials and aqueous solutions. Both temperature and pressure should be used to monitor the process. The temperature recorder should normally be independent of the controller, and there should be an independent temperature indicator, the reading from which is routinely checked against the chart recorder during the sterilization period. For sterilizers fitted with a drain at the bottom of the chamber, it may also be necessary to record the temperature at this position, throughout the sterilization period. There should be regular leak tests on the chamber when a vacuum phase is part of the cycle.
- The items to be sterilized, other than products in sealed containers, should be wrapped in a material which allows removal of air and penetration of steam but which prevents re-contamination after sterilization. All parts of the load should be in contact with the sterilizing agent at the required temperature for the required time.
- Care should be taken to ensure that steam used for sterilization is of suitable quality and does not contain additives at a level which could cause contamination of product or equipment.

### **Sterilization By Dry Heat:**

- The processes used should include air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. Any air admitted should be passed through a HEPA filter. Where this process is also intended to remove pyrogens, challenge tests using endotoxins should be used as part of the validation.

## **Sterilization By Radiation:**

- Radiation sterilization is used mainly for the sterilization of heat-sensitive materials and products. Many pharmaceutical products and some packaging materials are radiation-sensitive, so this method is permissible only when the absence of deleterious effects on the product has been confirmed experimentally. Ultraviolet irradiation is not an acceptable method for terminal sterilization.
- If radiation sterilization is carried out by an outside contractor, the manufacturer has the responsibility of ensuring that the requirements of the point mentioned above are met, and that the sterilization process is validated. The responsibilities of the radiation plant operator (e.g. for the right dose) should also be specified.
- During the sterilization procedure the radiation dose should be measured. For this purpose, dosimeters that are independent of dose rate should be used, giving a quantitative measurement of the dose received by the product itself. Dosimeters should be inserted in the load in sufficient number, and close enough together to ensure that there is always a dosimeter in the chamber. Where plastic dosimeters are used, they should be used within a time-limit of the calibration. Dosimeter absorbances should be read within a short period after exposure to radiation. Biological indicators maybe used only as additional control. Radiation-sensitive colour discs maybe used to differentiate between packages that have been subjected to irradiation and those that have not; they are not indicators of successful sterilization. The information obtained should constitute part of the batch record.
- Validation procedures should ensure that consideration is given to the effect of variations in the density of the packages.
- Handling procedures should prevent any mix-up between irradiated and non-irradiated materials. Each package should carry a radiation-sensitive indicator to show whether or not it has been subjected to radiation treatment.
- The total radiation dose should be administered within a predetermined time span.

## **Sterilization by Ethylene Oxide:**

- Various gases and fumigants maybe used for sterilization. Ethylene oxide should be used only when no other method is practicable. During process validation it should be shown that the gas has no damaging effect on the product and that the conditions and time allowed for degassing are such as to reduce any residual gas and reaction products to defined acceptable limits for the type of product or material. These should be incorporated into specifications.
- Direct contact between gas and microbial cells is essential; precautions should be taken to avoid the presence of organisms likely to be enclosed in material such as crystals or dried protein. The nature and quantity of packaging materials can significantly affect the process.
- Before exposure to the gas, materials should be brought into equilibrium with the humidity and temperature required by the process. The time required for this should be balanced against the opposing need to minimize the time before sterilization.
- Each sterilization cycle should be monitored with suitable biological indicators, using the appropriate number of test pieces distributed throughout the load. The information so obtained should form part of the batch record.
- Biological indicators should be stored and used according to the manufacturer's instructions, and their performance checked by positive controls.
- For each sterilization cycle, records should be made of the time taken to complete the cycle, of the pressure, temperature, and humidity within the chamber during the process, and of the gas concentration. The pressure and temperature should be recorded throughout the cycle on a chart. The records should form part of the batch records.
- After sterilization, the load should be stored in a controlled manner under ventilated conditions to allow residual gas and reaction products to fall to the defined level. This process should be validated.

### **Filtration of medicinal products which cannot be sterilized in their final container:**

17. The following conditions apply:

- If the product cannot be sterilized in the final container, solutions or liquids can be filtered through a sterile filter of nominal pore size of 0.22microns (or less), or with at least equivalent microorganism retaining properties, into a previously sterilized container.
- Such filters can remove most bacteria and moulds, but not all viruses or mycoplasma.
- The final sterile filtration should be carried out as close as possible to the filling point.
- Fibre shedding characteristics of filters should be minimal.
- The integrity of sterilized filter should be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble point, diffusive flow or pressure hold test.
- The same filter should not be used for more than one working day unless such use has been validated.
- The filter should not affect the product by removal of ingredient from it or by release of substances into it.

### **Finishing of sterile products:**

18. The following conditions apply:

- Containers should be closed by appropriate validated methods.
- Samples of other containers should be checked for integrity according to appropriate procedures.
- Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, pre-determined period.
- Filled containers of parenteral products should be inspected individually for extraneous contamination or other defects.
- Inspection methods should be validated and the performance of the equipment checked at intervals.
- Results should be recorded.

### **Quality Control:**

19. The following conditions apply:

- The sterility test applied to the finished product should only be regarded as the last in a series of control measures by which sterility is assured.
- The test should be validated for the product(s) concerned.
- Samples taken for sterility testing should be representative of the whole of the batch, but should in particular include samples taken from parts of the batch considered to be the most at risk of contamination.

## **2. Manufacture of Biological Medicinal Products for Human Use**

### **Principle:**

- The manufacture of biological medicinal products involves certain specific considerations arising from the nature of the products and the way they are produced, controlled and administered which require additional precaution.
- Biological medicinal products are produced by methods involving biological processes and materials, such as cultivation of cells or extraction of material from living organisms which provide good substrates for growth of microbial contamination.
- In-process controls therefore take on a great importance in the manufacture of biological medicinal products because of the inherent variability of the biological processes and hence the variability of the range and nature of the by-products produced.

### **Personnel:**

1. All personnel including those concerned with cleaning, maintenance or quality control, employed in areas where biological medicinal products are manufactured should receive additional training specific to the products manufactured and to their work. PLUS they should be given relevant information and training in hygiene and microbiology.
2. Production and quality control personnel should have adequate background in relevant scientific disciplines such as chemistry, pharmacy, pharmacology, biology, medicine, virology, immunology, bacteriology, biometry, and veterinary medicines together with sufficient practical experience in their work field.
3. All personnel involved in production, maintenance, testing and animal care (and inspectors) should be vaccinated where necessary and have regular health checks.
4. Visitors should be generally excluded from production areas.
5. Any changes in the immunological status of personnel which could adversely affect the quality of the product should preclude work in the



production area. Production of BCG vaccine and tuberculin products should be restricted to staff who are carefully monitored by regular checks of immunological status or chest x-ray.

6. In the course of a working day, personnel should not pass from areas where exposure to live organisms or animals is possible to areas where other products or different organisms are handled. If such passage is unavoidable, clearly defined decontamination measures, including change of clothing and shoes and, where necessary, showering should be followed by staff involved in any production process.

### **Premises and equipment:**

- The degree of environmental control of particulate and microbiological contamination of production premises should be adapted to the product and the production step, bearing in mind the level of contamination of the starting material and the risk to the finished product.
- The risk of cross-contamination between biological medicinal products especially during those stages of the manufacturing process in which live organisms are used, may require additional precautions with respect to the facilities and equipment. The nature of the product as well as the equipment used will determine the level of segregation needed to avoid cross-contamination.
- In principle, dedicated facilities should be used for the production of BCG vaccine and for the handling of live organisms used in production tuberculin products.
- Dedicated facilities should be used for the handling of *Bacillus anthracis*, of *Clostridium botulinum*, and of *Clostridium tetani* until the inactivation process is accomplished.
- Production on a campaign basis maybe acceptable for other spore-forming organisms provided that the facilities are dedicated to this group of products and not more than one product is processed at any one time.
- Simultaneous production in the same area using closed systems of biofermenters maybe acceptable for products such as monoclonal antibodies and products prepared by r-DNA techniques.

- Processing steps after harvesting may be carried out simultaneously in the same production area provided that adequate precautions are taken to prevent cross-contamination. For killed vaccines and toxoids, such parallel processing should only be performed after inactivation of the culture or after detoxification.
- Positive pressure areas should be used to process sterile products but negative pressure in specific areas at point of exposure of pathogens is acceptable for containment reasons.
- Pipework systems, valves and vent filters should be properly designed to facilitate cleaning and sterilization. The use of "clean in place" and "sterilize in place" systems should be encouraged. Valves on fermentation vessels should be hydrophobic and validated for their scheduled life span.
- Primary containment should be designed and tested to demonstrate freedom from leakage risk.
- Air filtration units should be specific to the processing area concerned and re-circulation of air should not occur from areas handling live pathogenic organisms.
- The layout and design of production areas and equipment should permit effective cleaning and decontamination e.g. by fumigation. The adequacy of cleaning and decontamination procedures should be validated.
- the equipment used during handling of live organisms should be designed to maintain cultures in a pure state and uncontaminated by external sources during processing.
- effluents which may contain pathogenic microorganisms should be effectively decontaminated.
- Interior surfaces (walls, floors, and ceilings) shall be smooth and free from cracks; they shall not shed matter and shall permit easy cleaning and disinfection. Drains should be avoided wherever possible and, unless essential, should be excluded from aseptic areas. Where installed they should be fitted with effective, easily cleanable traps and with breaks or prevent back-flow. The traps may contain electrically operated heating devices to other means of disinfection. Any floor channels should be open, shallow and easily cleanable and be connected

to drains outside the area in a manner that prevents ingress of microbial contaminants.

- Sinks shall be excluded from aseptic areas. Any sink installed in other clean areas shall be of suitable material such as stainless steel, without an overflow, and be supplied with water of potable quality. Adequate precautions shall be taken to avoid contamination of the drainage system with dangerous effluents. Airborne dissemination of pathogenic microorganisms and viruses used for production and the possibility of contamination by other types of viruses or substances during the production processes, including those from personnel, shall be avoided.
- Lighting, heating, ventilation and, if necessary, air-conditioning should be designed to maintain a satisfactory temperature and relative humidity, to minimize contamination and to take account of the comfort of personnel working in protective clothing. Buildings shall be in a good state of repairs. The condition of the buildings should be reviewed regularly and repairs carried out when and where necessary. Special care should be exercised to ensure that building repair or maintenance operations do not compromise products. Premises should provide sufficient space to suit the operations to be carried out, allowing an efficient flow of work and effective communication and supervision. All buildings and rooms shall be clean and sanitary at all times. If rooms intended for the manufacture of biological substances are used for other purposes, they shall be cleaned thoroughly and, if necessary, sanitized before the manufacture of biological substances is resumed. Areas used for processing animal tissues' materials and microorganisms not required for the current manufacturing process and performing tests involving animals or microorganisms must be separated from premises used for manufacturing sterile biological products and have completely separate ventilation systems and separate staff.

### **Animal Quarters and Care :**

1. Animals are used for the manufacture of a number of biological products e.g. polio vaccine (monkeys), snake anti-venom (horses and goats), rabies vaccine (rabbits, mice and hamsters). In addition, animals may be used in the quality control of most sera and vaccines e.g. pertussis vaccine (mice), pyrogenicity (rabbits), BCG vaccine (Guinea-pigs).
2. Quarters for animals used in production and control of biological products should be separated from the production and control areas.
3. The health status of animals from which some starting materials are derived and those used for quality control and safety testing should be monitored and recorded.
4. Staff employed in such areas must be provided with special clothing and changing facilities.

### **Documentation:**

1. Specifications for biological starting materials may need additional documentation on the source, origin, method of manufacture and controls applied, particularly microbiological controls.
2. Specifications are routinely required for intermediate and bulk biological medicinal products.

### **Production:**

#### **Starting Materials:**

1. The source, origin and suitability of starting materials should be clearly defined.
2. where sterilization of starting materials is required, it should be carried out where possible by heat.
3. Other appropriate methods maybe used for inactivation of biological materials where necessary.

**Seed lot and cell bank system:**

1. In order to prevent the unwanted drift of properties which might ensue from repeated subcultures or multiple generations, the production of biological medicinal products obtained by microbial culture, cell culture or propagation in embryos and animals should be based on a system of master and working seed lots and/or cell banks.
2. The number of generations (doubling, passages) between the seed lot or cell bank and the finished product should be consistent with the marketing authorization dossier. Scaling up of the process should not change this fundamental relationship.
3. Seed lots and cell banks should be adequately characterized and tested for contaminants. Their suitability for use should be further demonstrated by the consistency of the characteristics and quality of the successive batches of product. Seed lots and cell banks should be established, stored and used in such a way as to minimize the risks of contamination or alteration.
4. Establishment of the seed lot and cell bank should be performed in suitably controlled environment to protect the seed lot and the cell bank and, if applicable, the personnel handling it. During the establishment of the seed lot and cell bank, no other living or infectious material (e.g. virus, cell lines, or cell strains) should be handled simultaneously in the same area or by the same persons.
5. Evidence of the suitability and recovery of the seeds and banks should be demonstrated. Storage containers should be hermetically sealed, clearly labeled and kept at an appropriate temperature. An inventory should be meticulously kept. Storage temperature should be recorded continuously for freezers and properly monitored for liquid nitrogen. Any deviation from set limits and any corrective action taken, should be recorded.
6. Only authorized personnel should be allowed to handle the material and this handling should be done under the supervision of a responsible person. Access to stored material should be controlled. Different seed lots or cell banks should be stored in such a way as to avoid confusion or cross-contamination. It is desirable to split the seed oil and cell banks and to store the parts at different locations so as to minimize the risks of total loss.
7. All containers or master or working cell banks and seed lots should be treated identically during storage. Once removed from storage, the containers should not be returned to the stock.

## **Operating Principle:**

1. The growth promoting properties of culture media should be demonstrated.
2. The addition of materials or cultures to the fermenters and other vessels and the taking of samples should be carried out under carefully controlled conditions to ensure that absence of contamination is maintained.
3. Care should be taken to ensure that vessels are correctly connected when addition or sampling take place.
4. Media should be sterilized where possible.
5. Strict measures should be taken to avoid the risk of contamination of treated by untreated products when virus inactivation or removal process is performed during manufacture.
6. A wide variety of equipment used for chromatography should generally be dedicated to the purification of one product and should be sterilized or sanitized between batches. The use of one equipment at different stages of processing should be discouraged.
7. Labeling:
  - a. All products shall be clearly identified by labels. The labels used must remain permanently attached to the containers under all storage conditions and an area of the container should be left uncovered to allow inspection of the contents. If the final container is not suitable for labeling (for example a capillary tube), it should be in a labeled package.
  - b. The information given on the label on the container and the label on the package shall be approved by the national control authority.
  - c. The label on the container shall show:
    - i. The name of the drug product.
    - ii. A list of the active ingredients and the amount of each present, with a statement of the net contents, e.g. number of dosage units, weight or volume.
    - iii. The batch or final lot number assigned by the manufacturer.
    - iv. The expiry date.
    - v. Recommended storage conditions or handling precautions that maybe necessary.
    - vi. Directions for use, and warnings and precautions that maybe necessary.

- vii. The nature and amount of any substance used in the preparation of the biological product that is likely to give rise to an adverse reaction in some recipients.
  - viii. The name and address of the manufacturer or the company and/or the person responsible for placing the drug on the market.
  - d. The label on the package shall, in addition to the information shown on the label on the container, show at least the nature and amount of any preservative or additive in the product.
  - e. The leaflet in the package should provide instructions for the use of the product, and mention any contra-indication or potential adverse reactions.
8. Lot processing records (protocols) and distribution records:
- a. Processing records of regular production lots must provide a complete account of the manufacturing history of each lot of a biological preparation, showing that it has been manufactured, tested, dispensed into containers and distributed in accordance with the licensed procedures.
  - b. A separate processing record should be prepared for each lot of biological product, and should include the following information:
    - i. The name and dosage of the product
    - ii. The date of manufacture
    - iii. The lot identification number
    - iv. The complete formulation of the lot, including identification of seed or starting materials.
    - v. The batch number of each component used in the formulation.
    - vi. The yield obtained at different stages of manufacture of the lot.
    - vii. A duly signed record of each step followed, precautions taken and special observations made throughout the manufacture of the lot.
    - viii. A record of all in-process control tests and of the results obtained.
    - ix. A specimen of the label.
    - x. Identification of packaging materials, containers and closures used.

- xi. A dated signature of the expert responsible for approving the manufacturing operations.
  - xii. An analytical report, dated and signed by the responsible expert, showing whether the lot complies with the specifications described in the standard operating procedure registered with the national control authority.
  - xiii. A record of the decision regarding the release or rejection of the lot by the quality control department and, if the lot is rejected, a record of its disposal or utilization.
- c. The records shall be of a type approved by the national control authority. They shall be retained for at least 2 years after the expiry date of a lot or batch of a biological product and be available at all times for inspection by national control authority.
  - d. Records must make it possible to trace all steps in the manufacture and testing of a lot, and should include records of sterilization of all apparatus and materials used in its manufacture. Distribution records must be kept in a manner that permits rapid recall of any particular lot, if necessary.

### **Quality Control:**

1. In-process controls play a specially important role in ensuring the consistency and the quality of the biological medicinal products. These controls are crucial but cannot be carried out on the finished product. They should be performed at an appropriate stage of production.
2. Continuous monitoring of certain production processes is necessary, e.g. fermentation.



### **3. Medicinal Products Derived from Human Blood or Human Plasma**

#### **Principle:**

The starting materials for this type of medicinal products include the source material which are derived from human blood or plasma such as cells or fluids. These medicinal products have certain features arising from the biological nature of the source material e.g. disease-transmitting agents, especially viruses, may contaminate the source material.

Hence, the safety of these products relies on the control of the source material and their origin as well as on the subsequent manufacturing procedures including virus removal and inactivation.

Necessary measures should be taken to prevent the transmission of infectious diseases by these products.

Medicinal products derived from human blood and plasma do not cover blood components used in transfusion medicine.

#### **Glossary:**

- *Blood*: Whole blood collected from a single donor and processed either for transfusion or further manufacturing.
- *Blood Components*: Therapeutic components of blood (red cells, white cells, plasma, platelets) that can be prepared by centrifugation, filtration and freezing using conventional blood bank methodology.

### **Quality Management:**

1. Quality assurance should cover all stages leading to the finished product from collection to storage, transport, processing, quality control and delivery of the finished product.
2. Blood or plasma used as a source material for the manufacture of medicinal products should be collected by establishments and be tested in labs which are subject to inspection and approval by a competent authority.
3. Procedure to determine the suitability of individuals to donate blood and plasma and the results of the testing of their donations should be documented by the collection establishment and should be available to the manufacture of the medicinal product.
4. Monitoring of the quality of medicinal products derived from human blood or plasma should be carried out in such a way that any deviations from the quality specifications can be detected.
5. Medicinal products derived from human blood or plasma which have been returned unused should normally not be re-issued.

### **Premises and Equipment:**

1. The premises used for the collection of blood or plasma should be of suitable size, construction and location to facilitate their proper operation, cleaning and maintenance.
2. Manufacturing, collection and testing equipment should be designed, qualified and maintained to suit its intended purpose, and should not present any hazard. Regular maintenance and calibration should be carried out and documented according to established procedures.
3. In the preparation of plasma-derived medicinal products, viral inactivation or removal procedures are used and steps should be taken to prevent cross-contamination of treated with untreated products.
4. Dedicated and distinct premises and equipment should be used for for treated products.

### **Blood and Plasma Collection:**

1. A standard contract is required between the manufacturer of the medicinal product derived from human blood or plasma and the blood/plasma collection establishment or organization responsible for collection.
2. Each donor must be positively identified at reception and again before venepuncture.
3. The method used to disinfect the skin of the donor should be clearly defined and shown to be effective.
4. Donation number labels must be re-checked independently to ensure that those on blood packs, sample tubes and donation records are identical.

### **Traceability and Post Collection Measures:**

1. There must be a system in place which enables the path taken by each donation to be traced, both forward from the donor and back from the finished medicinal product, including the customer (hospital or healthcare professional). It is normally the responsibility of this customer to identify the recipient.
2. Post-collection measures: A standard operating procedure describing the mutual information system between the blood/plasma collection establishment and the manufacturing/fractionation facility should be set up so that they can inform each other if:
  - a. the donor did not meet the relevant health criteria.
  - b. a subsequent donation from a donor previously found negative for viral markers is found positive for any viral marker.
  - c. The donor has developed an infectious disease caused by an agent potentially transmissible by plasma-derived products (HBV, HCV, HAV, and other non-A, non-B, non-C hepatitis virus, HIV1 and 2 and other agents in the light of current knowledge)
  - d. the donor develops Creutzfeldt-Jacob disease (CJD or vCJD)
  - e. the recipient of blood or blood component develops post-transfusion/infusion infection which can be traced back to the donor.

3. In the event of any of the above, a re-assessment of the batch documentation should always be carried out. The need for withdrawal of a batch should be carefully considered, taking into account criteria such as the transmissible agent involved, the size of the product and its manufacturing method.
4. Where there are indications that a donation contributing to a plasma pool was infected with HIV or Hepatitis A, B or C, the case should be referred to the relevant competent authority(ies) responsible for the authorization of the medicinal product and the company's view regarding continued manufacture from the implicated pool or of the possibility of withdrawal of the products should be given.

### **Production and Quality Control:**

1. Before any blood and plasma donations or any product derived there-from are released for issue and/ or fractionation, they should be tested, using validated test method of suitable sensitivity and specificity, for the following markers of specific disease-transmitting agents:
  - HBsAG
  - Antibodies to HIV1 and HIV2
  - Antibodies to HCV

### **If a repeat-reactive result is found in any of these tests, the donation is not acceptable.**

1. The specified storage temperature of blood, plasma and intermediate products when stored and during transportation from collection establishment to manufacturers or between different manufacturing sites, should be checked and validated. The same applies to the delivery of these products.
2. The labels on single units of plasma stored for pooling and fractionation should bear the identification number of the donation, the name and address of the collection and establishment of the references of the blood transfusion service responsible for preparation, the batch number of the container, the storage temperature, the total volume or weight of plasma, the type of anticoagulant used and the date of collection and/or separation.
3. In order to minimize the microbiological contamination of plasma for fractionation or the introduction of foreign material, the thawing and

pooling should be performed at least in a grade D clean area, wearing the appropriate clothing and in addition face masks and gloves should be regularly worn.

4. Methods for clearly distinguishing between products or intermediates which have undergone a process or virus removal or inactivation, from those which have not, should be in place.
5. Validation of methods used for virus removal or inactivation should not be conducted in the production facilities in order not to put the routine manufacture at any risk of contamination with the viruses used for validation.

### **Retention Samples:**

1. Where possible, samples of individual donations should be stored to facilitate any necessary look-back procedure..
2. Samples of each pool of plasma should be stored under suitable conditions for at least one year after the expiry date of the finished product with the longest shelf life.

### **Disposal of rejected blood, plasma or intermediate:**

There should be a standard operating procedure for safe and effective disposal of blood, plasma or intermediate products.

#### **4. Manufacture of Liquids, Creams and Ointments**

##### **Principle:**

Liquids, creams and ointments maybe particularly susceptible to microbial contamination(and others) during manufacture. Therefore, special measures must be taken to prevent any contamination.

##### **Premises and Equipment:**

1. The use of closed systems for processing and transfer is recommended in order to protect the product from contamination. Production areas where the product or open containers are exposed should normally be effectively ventilated with filtered air.
2. Tanks, containers, pipework, and pumps should be designed and installed so that they may be readily cleaned and if necessary sanitized.
3. Equipment design should include a minimum of dead-legs or sites where residues can accumulate and promote microbial proliferation.
4. High quality stainless steel is often the material of choice for parts coming into contact with the product. Glass apparatus should be avoided where possible.

##### **Production:**

1. The chemical and microbiological quality of water used in the production should be specified and monitored.
2. Water systems should be carefully maintained to avoid the risk of microbial proliferation.
3. After chemical sanitization of the water systems, a validated flushing procedure should be followed to ensure that the sanitizing agent has been effectively removed.
4. The quality of materials received in bulk tankers should be checked before they are transferred to bulk storage tanks.
5. Care should be taken when transferring materials via pipelines to ensure that they are delivered to their correct destination.

6. Materials likely to shed fibers or other contaminants, like cardboards or wooden pallets, should not enter the areas where products or clean containers are exposed.
7. Homogeneity of mixtures, suspensions, etc should be maintained at the start of, during, and at the end of the filling process.
8. Mixing and filling processes should be validated.
9. When the finished product is not immediately packaged, the maximum period of storage and the storage conditions should be specified and adhered to.

## **5. Manufacture of Solid Dosage Form**

### **Introduction:**

The GMP inspection of a solid dosage form line follows the same principles and rules that are previously mentioned for the other dosage forms. In this section, we will focus our attention on additional aspects of the GMP inspection which should be realized and covered by the inspection team when they are performing inspection on a solid dosage form manufacturer.

### **Principle**

This GMP-DR guide provides information regarding the inspection and evaluation of the manufacturing and control processes used to manufacture solid oral dosage form pharmaceutical products. The inspection team should observe facilities, equipment and processes to put data review in the proper context. It is also important that raw data, including validation and laboratory logbooks be audited or reviewed to verify accuracy and authenticity. The inspection process should cover three phases:

## **PRODUCT DEVELOPMENT**

### **A. PRODUCT DEVELOPMENT REPORTS**

- Most companies have used product development reports, technology transfer reports, and others to summarize the scientific data that justifies the product and process.
- The product development report should satisfy the needs of the company. Therefore, there is no specific format for the contents of the report.
- It is suggested that the company develops a product development SOP which describes the development process, the documentation requirements, and the individuals responsible for approving the filed



process. This SOP can be brief and again there is no legal requirement that companies produce such an SOP.

- Inspectors must not list the absence and/or the poor quality of a product development report . They should list or include the inadequacy of data to support the filed process and specific Master Formula filed. It is not a GMP deficiency nor is it a filing requirement to have a formal Development Report. Investigators should review product development reports since they will reduce the time required to inspect the process.

The development data found in these reports should include the following:

### **1. Drug Substance Characterization**

- Characterization of the chemical and physical properties of the drug substance is one of the most important steps in the development of a solid dosage form. The literature, and actual experience demonstrates, that the physical quality, e.g., particle size of raw materials, can sometimes produce a significant impact on the availability and clinical effect of a dosage form drug. Therefore, it is appropriate that the physical characteristics of a drug substance be characterized, that the impact of the physical characteristics be determined and that a specification for the bulk drug product be established if necessary.
- Therefore, the finished dosage form the manufacturer must perform the appropriate test to characterize the drug substance chemically and physically and establish appropriate specifications. This may require developing analytical methods to identify impurities. In some cases this information can be obtained from literature searches. Remember that the safety of the drug may be based upon the type and level of impurities and different physical characteristics may affect dissolution or content uniformity.
- Inspectional coverage should be given to the physical characteristics of raw materials, especially bulk drug substances, since they frequently affect the performance of the dosage form in which they are incorporated. This is particularly important for those drug substances that are poorly soluble in water.

- It is widely recognized that when discussing in-vivo release rates and drug absorption rates, fast, immediate release is not always best. For some "immediate" release drug products, such as carbamazepine tablets, a slower release is desired. Therefore, it is frequently desirable to have minimum and maximum particle size specifications to control the release rate. For example, micronizing or milling a drug substance and providing greater surface area of the substance may also result in faster dissolution and possibly faster absorption and higher blood levels. Such changes to "improve" the dissolution may not always be desired.
- In addition to release or dissolution, variation in particle size, particle shape, and/or bulk density can also have an effect on the uniformity of dosage forms, particularly those manufactured by direct compression or direct encapsulation.
- Particulate solids, once mixed, have a tendency to segregate by virtue of differences in the shape, size and density (other variables are also important) of the particles of which they are composed. This process of separation occurs during mixing, as well as during subsequent handling of the completed mix. Generally, large differences in particle size, density or shape within the mixture result in instability in the mixture. The segregation process normally requires energy input and can be reduced following mixing by careful handling.
- Some manufacturers have established wide ranges for specifications. Investigators should review these specifications from a GMP and validation perspective. Even though a wide range for a physical specification, such as particle size or surface area may be established in a filing, it is expected that such ranges be verified in the validation of the process. In a recent court decision the judge ruled that companies cannot hide behind the approval of processes listed in an application when these processes do not work. In other words the approval of the filing has no impact on processes that do not perform consistently. For example, in a filed process it was determined that particle size would have no effect on drug absorption and dissolution and a wide range particle size specification was established. However, in the GMP review, it was found that variation in particle size had a major effect on

content uniformity. Therefore, a tighter particle size specification had to be established.

- Control of the physical characteristics of the excipient is also important because variations in such characteristics may also affect the performance of the dosage form. Changes in particle size of some excipients, for example, may affect content uniformity. In other cases, a change in the supplier of an excipient or lubricant may affect dissolution or bioavailability. In fact, the release of the active ingredients in some products is "timed" by varying lubricant blending time and concentration. Such changes in excipients illustrate the deficiencies with the utilization of retrospective validation because, for such validation to be satisfactory, control of all parameters and key steps in the process are necessary.
- The control of mixing times and physical characteristics of all ingredients is critical to successful validation of all formulations and processes. A major question that must be addressed is the need for testing physical characteristics (particle size) for each batch of excipient. For many single source excipients, particle size is a supplier specification and is usually tightly controlled. Having established a specification and not testing each lot of excipient upon receipt may be satisfactory in such cases. However, for some multi-source excipients and where the dosage formulator expects to shift sources of supply, there may be differences in physical characteristics (particle size) that may have an effect on dose uniformity and dissolution. Examine the practices with respect to the source of supply of the key excipients and determine if there is justification for the lack of testing lots of excipient for physical characteristics.

## **2. Manufacturing Procedures**

- Procedures used to manufacture development batches must be specific and well documented. This is necessary for scale-up and subsequent comparison to the commercial process.

### **3. In-process Testing**

- Specific specifications required to control the manufacturing process must be established and justified. This will require granulation studies which would include blend uniformity, sieve analysis, and moisture.

### **4. Finished Product Testing**

- Testing for the monograph standards such as content uniformity (when a specification applies), assay, hardness, friability, dissolution, and others are essential.

### **5. Stability**

- An evaluation of the stability data must be performed to approve the expiration date. The product development report should contain an evaluation of the stability data that has been obtained.
- During post-approval inspections stability data is reviewed by the field. Therefore, the inspector must audit underlying raw data and analytical worksheets to assure the accuracy and authenticity of stability data contained in summary reports.

## **B. PRE-APPROVAL INSPECTIONS**

- To evaluate the proposed manufacturing process, the following areas must be covered during the pre-approval inspection:

### **1. Master Formula**

- This document must include specific manufacturing directions for the full scale commercial process including in-process and finished product specifications.

## **2. Inspection of the Facilities**

- It is important that you physically inspect the facility to assure that the area and the ancillary equipment such as air handling and water systems are suitable for the proposed manufacturing process. Construction of new walls, installation of new equipment, and other significant changes must be evaluated for their impact on the overall compliance with GMP requirements. This includes facilities used for development batches and to be used for full-scale production batches.

## **3. Raw Materials**

- Review the information contained in the Raw Material sections under previous GMP sections, as they follow the same rules.

## **4. Laboratory**

- The inspection of a laboratory requires the use of observations of the laboratory in operation and of the raw laboratory data to evaluate compliance with GMP's and to specifically carry out the commitments in an application or DMF.
- Evaluate raw laboratory data, laboratory procedures and methods, laboratory equipment, and methods validation data to determine the overall quality of the laboratory operation and the ability to comply with GMP regulations.

## **5. Equipment**

- At the time of the pre-approval inspection we expect that the equipment is in place and qualified. New products, particularly potent drug products, can present cleaning problems in existing equipment. Manufacturers must validate their cleaning processes for the new drug/dosage form.

## **C. Post-Approval Prospective Validation Inspections**

- Several parameters must be considered when evaluating the validation of an oral solid dosage form manufacturing process. For example there are at least seven major areas that must be included:
  1. Raw Materials
  2. Manufacturing Procedures and Equipment
  3. Granulation/Mix Analysis
  4. In-Process Controls
  5. Test Results with Validated Methods
  6. Investigations/Product Failures
  7. Site Review

### **1. Raw Materials**

- Physical characteristics of raw materials can vary among manufacturers of drug substances and, on occasion, have varied from lot to lot from the same manufacturer. Upon examination of retain samples of the lots of raw material, obvious physical differences between the two lots may be observed.
- Review the raw material inventory records to evaluate the use of the drug substance in the manufacturing batches. Pay attention to the quantities and source of materials used and the testing performed.
- Inspections should cover the firm's data for the establishment of their physical specifications for drug substances. If the firm has no specification, or a very vague specification, they should be able to provide data to demonstrate that dissolution profiles and content uniformity will be satisfactory over a wide range of particle sizes. For example, a manufacturer may establish a specification of 90% of the particles must be less than 300 microns. For validation of this process, one would expect the use of micronized as well as material with particles close to 300 microns in size.

## **2. Manufacturing Procedures and Equipment**

- Regardless of the nature of the specificity of the manufacturing directions contained in the application, a detailed master formula with specific manufacturing directions and specifications must have been developed before any validation protocol is prepared and before the validation process begins. The basic premise of validation of a process is that a detailed process already exists which hopefully will be shown to perform consistently and produces products in compliance with predetermined specifications. Therefore, detailed manufacturing directions, specifying equipment and operating parameters must be specified in the master formula.

**The importance of specific written directions and specifications cannot be overemphasized. For example, problem areas may include:**

1. the failure to specify the amount of granulating solution, resulting in overwetting and dissolution failures of aged batches
2. the failure to specify the encapsulation machines and operating parameters, such as dosing discs, resulting in weight variation failures
3. the failure to specify the compression machine(s) and operating parameters, resulting in content uniformity failures

In addition to the concern about specific manufacturing directions, equipment presents its own set of unique problems which have to be considered in the control of the manufacturing and the validation processes. The following is a brief description of some issues associated with equipment:

### **a. Blenders**

- Many solid oral dosage forms are made by direct compression. There are generally two types of mixers - low energy and high energy. The low energy mixers represent the classical type of slow mixers, such as ribbon blenders, tumblers, and planetary pony pan. The high energy mixers include some basic features of the low energy mixer but also contain some type of high speed blade, commonly termed an intensifier bar or chopper.

## 1. Pony Pan Type

- This mixer has historically been used for the manufacture of wet granulations. Because of its open pan or pot, granulating agents, such as starch paste, could be added while mixing. Since it is usually open at the top to allow the mixing blades to penetrate the powder, mixing operations are usually dusty and can lead to potential cross-contamination problems.

The usefulness of these mixers is limited to wet granulating. With this type of mixer, there is good horizontal (side to side) blending. However, vertical (top to bottom) mixing does not occur. Powder placed in the mixer first will be poorly mixed. Segregation or un-mixing is also a recognized problem. To minimize this problem, some manufacturers have emptied the pan contents half-way through the mixing cycle in an attempt to turn the powder over at the bottom of the mixer. To alleviate the problem of the lack of mixing along the sides or walls of the pan, manufacturers have utilized a hand-held steel paddle at various times during mixing. This type of mixing is difficult to control and reproduce. Thus, it would be difficult to validate.

The potential for segregation and poor mixing along the sides and particularly the bottom of the pony blender makes this type of blender less desirable for the dry blending of granulations of drug products. Consequently, whenever such dry blending is encountered, the investigator should be alert to potential problems with blending validation and content uniformity. Whenever in-process samples of the granulation are collected as part of an investigation or inspection, the formula card along with the weight of the dosage unit to be manufactured is needed for calculations.

## 2. Ribbon Blender

- In the ribbon blender, powder is mixed both horizontally and vertically. Loading operations can be dusty. However, during the actual blending, it is enclosed, thereby limiting the amount of dust generated to the environment.



- The major and potentially the most serious problem with the ribbon blender is that there is a "dead-spot" or zone at the discharge valve in some of these blenders. To compensate for this "dead-spot", manufacturers have to recycle the powder from this area at some point during the mixing process. Obviously, there should be adequate and very specific directions and procedures for assuring this critical step is performed. Verify that this step is included in the directions.
- Another concern with this mixer is the poor mixing at the ends of the center horizontal mixing bar and at the shell wall because of blade clearance. The level of powder placed in this mixer is normally at the top of the outer ribbon blade, and as with other mixers, care must be taken not to overfill the mixer.
- Cleaning problems, particularly at the ends of the ribbon blender where the horizontal bar enters the blender, have been identified. If manufacturers do not disassemble and clean the seals/packing between batches, they should have data to demonstrate the absence of foreign contaminants between batches of different products processed in the blender.

### **3. Tumbler Blender**

- Common mixers of this type include the twin-shell and double cone. These mixers exert a gentle mixing action. Because of this mild action, lumps of powder will not be broken up and mixed. Powders may also clump due to static charges and segregation can occur. Low humidity can contribute to this problem. Blending under very dry conditions has been found to lead to charge build-up and segregation, while blending of some products under humid conditions has led to lumping. More so than with other mixers, powder charge levels should not exceed 60 to 65% of the total volume of the mixer.
- Fabricators of tumbler type blenders identify the volume as the actual working capacity and not the actual volume of the blender. It is important to correlate the bulk density of the granulation with the working capacity of the blender.

#### **4. High Shear (high energy) Mixers**

- These mixers are highly efficient and ideally suited for wet granulations. End point of wet granulations can be determined by a measurement on a gauge of the work needed to agitate the blend. The mixing vessel is enclosed, and dust only enters the environment when loading.
- One of the problems associated with these mixers is the transfer or conversion of products blended in the older types of mixers to these blenders. Mixing times are going to be different, and the physical characteristics of the blend may also be different.
- These mixers are very efficient. For wet granulations, it is important to control the rate and amount of addition of the solvent. Because of their efficiency, drug substance may partially dissolve and re-crystallize upon drying as a different physical form.
- The presence of an intensifier bar in the center of the blender which rotates at very high speed breaks down smaller, harder agglomerates. A major disadvantage of this type of blender is that the extremely high speed of the intensifier bar generates considerable heat that can sometimes result in charring of some sugar base granulations. It should be pointed out that these same comments are applicable to other high energy mixers which also rely on high speed choppers to disperse powders. Also, cleaning of the blender requires disassembly of the intensifier bar between products.

#### **5. Plastic Bag**

- Any discussion of mixers would not be complete without addressing the plastic bag. Firms have resorted to the blending or manufacture of a trituration in a plastic bag. Obviously, it is very difficult to reproduce such a process, and there is the potential for loss of powder as a result of breakage or handling. The use of a plastic bag cannot be justified in the manufacture of a pharmaceutical product.

- When the plastic bag has been used, directions are usually not specific, and one would not know by reading the directions that a plastic bag was employed. In a recent inspection, a firm was noted to manufacture a small 5 kg. size batch of a tranquilizer. Because all of the firm's blenders were of much larger capacity, an inquiry was made as to the mixer employed. Although the processing records indicated a large blender was employed, it was later determined that the batch was actually blended in a plastic bag.

#### **b) Dryers**

- There are two basic types of dryers. One is the oven dryer where the wet granulation is spread on trays and dried in an oven. The second dryer is the fluid bed dryer in which the wet granulation is "fluidized" or suspended in air. Generally, the fluid bed dryer yields a more uniform granulation with spherical particles. However, this may result in compression problems that may require additional compression force. It is not unusual to see manufacturers change from an oven dryer to the fluid bed dryer. However, such a change should be examined for equivalency with in-vitro testing such as hardness, disintegration and comparative dissolution and stability testing conducted.
- Other issues of concern with drying include moisture uniformity and cross contamination. Tray dryers present more moisture uniformity problems than fluid bed dryers. Obviously, a dryer should be qualified for heat uniformity and a program developed to assure moisture uniformity in granulations at the end point of drying. With respect to fluid bed dryers, moisture problems can occur if the granulation is not completely fluidized.
- Regarding cross contamination, oven dryers, particularly those in which air is re-circulated, present cross contamination problems because air re-circulates through a common filter and duct. For fluid bed dryers, the bag filters present cross-contamination problems. In order to minimize problems, manufacturers use product dedicated bags.

### **c) Tablet and Capsule Equipment**

- Another important variable in the manufacturing process is the tablet press or encapsulating machine. The newer dosage form equipment requires granulations with good flow characteristics and good uniformity. The newer tablet presses control weight variation by compression force and require a uniform granulation to function correctly. Setup of the microprocessor controlled tablet press usually includes some type of challenge to the system. For example, a short punch is sometimes placed among the other punches. If the press is operating correctly, it will alarm when the lower or high weight tablet is compressed.
- Different tablet compression equipment can cause dose uniformity, weight uniformity and hardness problems. For example, vibrations during tablet compression can cause segregation of the granulation in the feed hopper. Speed of the machine can affect fill of the die and tablet weight. Therefore, as previously discussed, it is important to have specific operating directions.
- Many unit operations now provide for blending in totes with discharge of the tote directly into tablet compression equipment. Because of segregation problems at the end of discharge, tablets from the end of compression should be tested for content uniformity. The use of inserts in totes has been shown to minimize segregation.
- With regard to the newer computer controlled tablet compression equipment, buckets of tablets are often rejected because of potential weight variation problems. The disposition of these tablets, as well as the granulation and tablets used to set up the press, should be investigated. Reworking processes must be validated.
- With regard to encapsulation operations, the hygroscopic nature of gelatin capsules and some of the granulations, requires humidity controls for storage of the empty capsules and their subsequent filling. Scale-up of capsule products has also presented some problems because of the different types of encapsulation equipment. When formulations were scaled-up to high speed encapsulation equipment, flow problems and poor weight variation resulted.

- As previously discussed, set-up and review of operating directions should be covered in inspections. Check the data used to qualify equipment and investigate the equipment log for this sorting machines to identify batches with weight problems that were processed in it. The data supporting the accuracy of equipment to reject low or high weight capsules should be reviewed.

#### **d) Coating Equipment**

- Many tablets are now coated with an aqueous film coat that is usually very soluble. Current technology provides for fixed sprays of the coating solution. The volume of coating solution, rate and temperature can be controlled by some of the more highly automated operations. However, many sugar coated, enteric coated and delayed release products exist where some portions of the coating process are not highly soluble and are performed manually. Generally, the shellac undercoat used for sugar coated tablets has presented disintegration/dissolution problems, particularly in aged samples.
- With respect to poor disintegration, there have been many problems attributed to the coating process. Again, the shellac undercoat hardens, and even sometimes cracks, resulting in poor dissolution.
- There have been many occasions when the coating process was not validated. The number of applications of coats, volume of coating solution in a specific application, and temperature of the solution during application are all parameters that need to be addressed. For example, the temperature of application and even heat during drying have been found to cause dissolution failures in aged tablets.
- Another problem associated with the coating process concerns the heat applied to products that are sensitive to heat. For example, it has been shown that estrogen tablets are heat sensitive and have exhibited stability problems. Thus, it is important to control this phase of the process.
- There are a few products, such as some of the antihistamine tablets, in which the drug substance is applied during the coating process. Other products require the active drug substance to be applied as a dust on

tacky tablets as part of the coating process. For these products, it is particularly important to apply the drug in the coating solution in many controlled applications.

- Examine processing records for specificity in the identification of critical steps in the coating process. Review the firm's data demonstrating that critical steps are consistent and reproducible.
- Again, it is important as part of the validation of these processes to demonstrate dose uniformity and dissolution and to control the parameters of the coating process.

### **3. Granulation/Mix Analysis**

- A critical step in the manufacture of an oral solid dosage form is the blending of the final granulation. If uniformity is not achieved at this stage, then one could assume that some dosage units would not comply with uniformity requirements. The major advantage of blend analysis (from a uniformity perspective) is that specific areas of the blender which have the greatest potential to be non-uniform can be sampled. This is particularly true of the ribbon type blender and planetary or pony type mixers.
- In some cases, such as for large or tumbler type blenders, it is impractical to sample from the blender directly. In such cases, granulations or blends could be sampled at the time of blender discharge or directly from drums. If sampling from drums, samples from the top, middle and bottom of each drum should be collected.
- In most cases sampling thieves are readily available for sampling the small quantities that need to be taken from key areas of the blender or the drums. If samples larger than one dosage unit must be collected, however, adequate provisions must be made to prevent excessive handling manipulation between the time of sampling and the time of analysis.
- Good science and logic would seem to dictate that sample sizes of the approximate equivalent weight of the dosage unit that should be sampled in order to test for uniformity. Large granulation sample sizes, such as one ounce will provide little information with respect to

uniformity. Generally, further mixing after sampling and prior to analysis occurs which yields misleading results.

- The acceptance criteria for granulation dose uniformity testing needs to be evaluated. If larger sample sizes are taken for assay to evaluate total composite assay, then the specific USP or filed criteria for assay should be used. This key issue needs to be examined during the inspection.
- In addition to analysis of blends for dose uniformity and potency, blends are tested for physical characteristics. A major physical parameter used to demonstrate equivalence between batches is the particle size profile.
- Particle size profiles are particularly important for the tablet made by a wet granulation process. The size and even the type of granule can affect the pore size in a tablet and have an effect on dissolution. For example, a recent dissolution failure was attributed to a change in the milling screen size, yielding a granulation with larger granules. Since it was a coated tablet, larger pores permitted increased penetration into the tablet by the coating solution, resulting in slower dissolution.
- Another test which is typically performed on the granulation, particularly when the wet granulation process is used, is loss-on-drying (LOD) and/or moisture content. If organic solvents are employed, then residual solvent residues are also tested. In the validation of a drying process, LOD levels are determined prior to, during and after drying in order to demonstrate times and levels. As with processing variables, levels (specifications) are established in the development phase with the validation phase used to confirm the adequacy of the process. As with other specifications and processes, the investigator should review the data used to support the drying process and determine the significance (if any) of variable drying times and levels.

#### **4. In-Process Testing**

- For the purpose of this document, in-process testing is the testing performed on dosage forms during their compression/encapsulation stages to assure consistency throughout these operations. For tablets, individual tablet weights, moisture, hardness (compression force) and

disintegration are performed. For capsules, individual weights and moisture are performed.

- In many of the validation reports reviewed, manufacturers have neglected to supply individual (not composite) dosage unit weights performed throughout compression/encapsulation. This is particularly important for capsule products which may exhibit weight variation problems. If not part of validation reports, the individual dosage unit weights should be reviewed.
- With regard to individual capsule weights, a major question that arises concerns acceptable levels. Since most USP assay limits are 90 to 110%, it would seem reasonable that each unit manufactured should comply with these specifications. It should be pointed out that 85 to 115% limits are established by the USP for variability in both blending and compression or encapsulation operations.
- With regard to moisture, some tablets have set up upon aging as a result of poor moisture control and inadequate specifications. For example, this has been shown to be a major problem with Carbamazepine tablets.

## **5. Test Results**

- Finished product testing, particularly assay, content uniformity and dissolution, should be reviewed. With regard to dissolution, it is important to review dissolution profiles.
- In the review of dissolution test results, it is important to eventually see results very close to 100% dissolution. In some cases, manufacturers will profile the dissolution results only to the specification. However, if lower, but still acceptable results are obtained (such as 85%), it is important to continue the test. This can be performed by increasing the speed of the apparatus. If a product completely dissolves, yet only results in a value of 85%, it may indicate some problem with the test. Likewise, high dissolution results (115%) also indicate some problem with the test. Obviously, unusual or atypical results should be explained in the validation report.



## **6. Investigations/Product Failures**

- In any process validation exercise, a basic objective is to prove that a process is satisfactory. Unfortunately, some processes are unsatisfactory and may sometimes yield unacceptable results. It is important, therefore, that when the final validation report is reviewed, all results, including failing results, be discussed and evaluated.
- When reviewing a validation report, the basis for concluding that a process is satisfactory, particularly those with failing results, should be evaluated.

## **7. Site Review**

A major aspect and possibly the most critical phase of the inspection process is the review of data at the manufacturer. Manufacturers present validation reports which appear to be very complete, however, when data was actually reviewed, failing batches are omitted without justification.