QUALITY ASSURANCE AND GOOD MANUFACTURING PRACTICES

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The basic concepts of Quality Assurance, Good Manufacturing Practice and Quality Control are inter-related. They are described here in order to emphasis their relationships and their fundamental importance to the production and control of medicinal products.

Quality Assurance is a wide ranging concept which covers all matters which individually or collectively influence the quality of a products. It is the sum total of the organized arrangements made with the object of ensuring that medicinal products are of the quality required for their intended use. Quality Assurance therefore incorporates Good Manufacturing Practice plus other factors out side the scope of this Guide.[1]

To emphasis their relationships and their fundamental importance to the production and control of medicinal product. Quality Assurance, ensure that medicinal product assure consistently produced are controlled to the quality standards according to Good Manufacturing Practice. Quality Assurance in order to monitor their implementation and respect of Good Manufacturing Practice and to propose any necessity corrective measures. To provide a mechanism to monitoring, evaluating, correcting and improving the activities of process.

Characteristics of a Quality Assurance plan include following:

Formalization in writing
Consideration of all aspects of preparation dispensing, environmental, testing, validation results.
Description of specific monitoring and evaluation activities.
Specification of how results are to be reported and evaluated.
identification of appropriate follow-up mechanism when action Limits or thresholds are exceeded.
Delineation for the individual responsible for each aspect of the Quality Assurance programme.

In the manufacture of drugs, overall control is essential to ensure that the consumer receives drugs of high quality. Haphazard operations cannot be permitted in the manufacture of substances that may be necessary to save life or to restore or preserve health.

Difficulties will undoubtedly arise in establishing the necessary criteria for the manufacture of drugs that will meet established specifications and that can therefore be used with confidence. Recommended practices for the manufacture of drugs of desired quality are set forth below. Adherence to these practices, complementing the various control tests followed from the beginning to the end of the manufacturing cycle, will contribute substantially to the manufacture of consistently uniform batches of high-quality drugs.

The manufacturer must assume responsibility for the quality of the drugs he produces. He alone can avoid mistakes and prevent mishaps by exercising adequate care in both his manufacturing and control procedures.

The good practices outlined below should be considered as general guides; whenever necessary, they may be adapted to meet individual needs provided the established standards of drug quality are still achieved. They are intended to apply to the manufacturing processes (including packaging and labelling) used in the production drugs in their finished dosage forms.

Sometimes it occurs that several firms cooperate in the production (including packaging and labelling) of the finished dosage forms of drugs. It may also occur that a finished, packed, and labelled drug is repacked and/or relabelled, giving it a new designation. It should be pointed out that since such procedures constitute part of a manufacturing operation, they should be subject to the relevant requirements proposed below.

The requirements set forth herein are intended to apply primarily to preparations for human administration. However, equal attention should be given to quality in the manufacture of veterinary preparations.

General Definitions

For the purposes of this document, the following definitions are adopted:

Drug:

Any substance or mixture of substances that is manufactured, sold, offered for sale, or represented for use (1) the treatment, mitigation, prevention, or diagnosis of disease,

an abnormal physical state, or the symptoms thereof in man or animal; or (2) the restoration, correction, or modification of organic functions in manor animal.

Manufacturing:

All operations involved in the production of a drug, including processing, compounding, formulating, filling, packaging, and labelling.

Starting materials:

All substances, whether active or inactive or whether they remain unchanged or become altered, that are employed in the manufacture of drugs.

Batch:

A quantity of any drug produced during a given cycle of manufacture. The essence of a manufacturing batch is its homogeneity.

Batch number:

A designation (in numbers and/or letters) that identifies the batch and that permits the production history of the batch, including all stages of manufacture and control, to be traced and reviewed.

Quarantine:

The status of a material that is set apart and that is not available for use until released.

Quality control:

All measures designed to ensure the output of uniform batches of drugs that conform to established specification of identity, strength, purity and other characteristics.

"Half-finished" product:

Any material or mixture of materials that must undergo further manufacture.

Personnel

Experts responsible for supervising the manufacture and quality control of drugs should possess the qualifications of scientific education and practical experience required by national legislation. Their education should include the study of an appropriate combination of (a) chemistry (analytical chemistry, biochemistry, etc.); (b) chemical engineering; (c) microbiology, (d) pharmaceutical sciences and technology (e) pharmacology and toxicology, (0 physiology and histology; and (g) other related sciences. They should also have adequate practical experience in the manufacture and

quality control of drugs. In order to gain such experience, a preparatory period may be required, during which they should exercise their duties under professional guidance. The scientific education and practical experience of experts should be such as to enable them to exercise of independent professional judgment, based on the application of scientific principles and understanding to the practical problems encountered in the manufacture and quality control of drugs.

Such experts should preferably not have any interest outside the manufacture's organization that (a) prevent or restrict their devoting the necessary time to their as-signed responsibilities or (b) may be considered to entail a conflict of financial interest. Finally, they should be given full authority and the facilities necessary to carry out their duties effectively.

In addition to the experts noted above, an adequate number of technically trained personnel should be available to carry out the manufacturing and quality control operations in accordance with established procedures and specification. All personnel should be motivated towards the establishment and maintenance of high-quality standards.

Premises

General

Drugs should be manufactured, processed, packaged labelled, and tested in premises that are suitable for these purpose?

In determining the suitability of premises regard should be paid to:

1) the compatibility of other manufacturing operations that may be carried out in the same or adjacent premises;

2) the adequacy of the working space, which should allow orderly and logical placement of equipment and materials so as to (a) minimize the risk of confusion between different drugs or their components, (b) control the possibility of cross-contamination by other drugs or substances and (c) minimize the risk of omission of any manufacturing or control stop;

3) those physical aspects of the premises that could effect the quality and safety of products: buildings should be so designed and constructed as to prevent the entry of animals and insects; interior surfaces (walls, floors and ceiling) should be smooth and free from craks, should not shed particulate matter, and should permit *easy* cleaning and if necessary disinfection;

4) lighting, heating and ventilation and, if necessary, air-conditioning required to maintain a satisfactory temperature and relative humidity that will not adversely affect the drug during manufacture and storage, nor the accuracy the accuracy and functioning of laboratory instruments.

Storage areas

The suitability of storage areas cannot be strictly specified in a manner that meets all possible contingencies. However, the following principles should be observed :[3]

1) storage areas should provide adequate space, suitable lighting, and should be arranged and equipped to allow dry, clean, and orderly placement of stored materials and products, whenever necessary under controlled conditions of temperature and humidity;

2) such areas should provide for suitable and effective separation of quarantined and other materials and products;

3) special and segregated areas should be available for storage of:
   a) substances presenting special risks of fire and explosion;
   b) hugely toxic, narcotic, and other dangerous drugs (these areas should be adequately protected against theft);
   c) rejected and recalled materials and products.

Starting materials

An inventory should be made of all starting materials to be used at any stage in the manufacture of drugs, and records should be kept of the supplier, the origin (if possible), date of receipt, date of analysis, date of release by the quality control department,[4] and their subsequent use in manufacture.

All such materials must be:

1) identified, and their containers examined for damage;
2) properly stored in quarantine;
3) properly sampled by the quality control department;
4) tested for compliance with requirements (all materials should be marked to indicate that they are under going testing); and
5) released from quarantine by the quality control department by means of written instructions.

Starting materials that are accepted or approved should be properly and conspicuously labelled as such, and should then be transferred, if necessarily, to areas designated for the storage of such materials.

All rejected starting materials should be conspicuously identified as such, and should be destroyed or returned to the supplier as soon as possible.

Special

For special purposes, such as the manufacture of drugs that are intended to be sterile but cannot be sterilized in their final containers, separate enclosed areas, specifically designed for the purpose, should be provide. These areas should be entered through an air-look and should be essentially dust-free and ventilated with an air supply through bacterial-retaining filters giving a pressure higher than in adjacent areas. Such filters should be checked for performance on installation and periodically thereafter. All surfaces in manufacturing areas should be designed to facilitate cleaning and disinfection.[5]

Routine microbe counts of the air in the areas described above should be carried out before and during manufacturing operations. The results of such counts should be checked against established standards, and adequate records of the counts should be maintained.

For the manufacture of drugs that can be sterilized in their final containers, the requirements given above are considered essential, with the exception of mandatory sterilization of air supplies. The design of areas used for this purpose should preclude the possibility that products intended for sterilization could be mixed with, or taken to be, products already sterilized. This may conveniently be effected by the use of double ended sterilization apparatus opening into separate and non- communicating areas.

Equipment

Manufacturing equipment should be designed, placed, and maintained in such a way as to:

1) be suitable for its intended use;
2) facilitate thorough cleaning wherever necessary;
3) minimize any contamination of drugs and their containers during manufacture; and
4) minimize the risk of confusion or the omission of a processing step such as filtration or sterilization.

Operating conditions within an apparatus used to sterilize products should be monitored by means recording devices, which should be initially calibrated and checked at approved intervals by approved methods. Suitable standardized microbiological indicators may be used to demonstrate the adequacy of the sterilization process.[6]

Manufacturing equipment and utensils should be thoroughly cleaned and, when necessary, sterilized, and should be maintained in accordance with specific written directions. When indicated, all equipment should be disassembled and thoroughly cleaned, to proclude the carry-over of drug residues from previous operations. Adequate records of such procedures should be maintained.

Equipment used for aseptic filling should be checked at suitable intervals by microbiological methods. Weighing and measuring equipment used in production and quality control should be calibrated and checked at suitable intervals by appropriate methods. Adequate records of such tests should be maintained.

Sanitation

Manufacturing premises should be maintained in accordance with the sanitary standards issued by the appropriate health authority. They should be clean and free from accumulated waste, orderly, and free from vermin. A written sanitation programme should be available, indicating:

1) areas to be cleaned, and cleaning intervals;
2) cleaning procedures to be followed and, if necessary, equipment and materials to be used for cleaning; and
3) Personnel assigned to and responsible for cleaning operations.

Eating, smoking, and unhygienic practices should not be permitted in manufacturing areas.

Sufficient, clean, well-ventilated toilet facilities, including facilities for hand-washing and rooms for changing clothes, should be available near working areas for the use of manufacturing personnel.

Manufacturing operations

Manufacturing operations and controls should be carried out under the super-vision of experts.[7]

1. Cleanliness

Before any manufacturing operation is begun, a check should be made to ensure all apparatus and equipment to be used in the operation has been cleaned an sterilized.

2. Equipment and containers

The contents of all vessels and containers used in manufacture and storage betw manufacturing stages must be identified by conspicuously placed and clearly leg labels, bearing the name and/or identification code of the processed materials and necessary batch identification data. Similar labels should be attached to mechar manufacturing equipment during its operation.

3. Precautions against contamination and confusion (mix-up)

All manufacturing operations should be confined to separate areas intended for s purposes, with complete equipment used exclusively in those areas, or measures sh be taken to ensure that neither cross-contamination nor confusion (mix-up) can occur.

In manufacturing areas, clean working garments should be worn over, or in place street clothing.

The manufacture of drugs intended to be sterile should be performed in a specially designed and constructed. Whenever the different operations are not physic separated, and there is a possibility that unsterilized and sterilized products sterilization should be a clear indication of whether or not their contents have sterilized.

Products that undergo sterilize operations should be protected from contaminatio using methods such a laminar-flow techniques, and by ensuring that personnel v clean, sterile gowns, head coverings, masks, rubber gloves, and shoe coverings. Be dressing and entering sterile areas, personnel must wash their hands with a suit disinfectant.

All dust-producing operations involving highly potent substances, particularly tibiotics, should be conducted in confined areas that are provided with adequate hausted system or that are maintained under appropriate pressure, so as to prevent cr contamination. Adequate precautions should be taken to prevent the recirculatio contaminated air.

4. Manufacturing personnel

No person known to be affected with a disease in a communicable form, or to be carrier of such a disease, and no person with open lesions on the exposed surface of

body, should be engaged in the manufacture of drugs. Manufacturing personnel should undergo periodic health checks. In order to prevent any impairment of health caused by the handling of hazardous or potent materials, manufacturing personnel should, whenever necessary, wear protective clothing, shoes, headgear, dust masks, etc., and such protective clothing should remain in the area in which it is used. In some instances, it may be necessary to have restrictions on the movement of personnel to and/or from special working areas.

5. Documents relating to manufacturing procedures

Documents relating to manufacturing procedures should be prepared for each drug under the direct supervision of experts who have the necessary authority. They should contain at least the following information for each drug:

1) its name and dosage form;
2) a description or identification of the final container(s); packaging material(s), and labels and, *where* applicable, of the closure(s) to be used;
3) the identity, quantity and quality of each starting materials to be used, irrespective of whether or not it appears in the finished drug (the permissible excess ("overage") that may be included in a formulated batch should be indicated);
4) the theoretical yields to be expected from the formulation at different stages of manufacture and the permissible yield limits;
5) detailed instructions for, and precautions to be taken in, manufacture and storage of the drug and of "half-finished" products; and
6) a description of all necessary quality control tests and analyses to be carried out during each stage of manufacture, including the designation of persons or departments responsible for or charged with the execution of such tests and analyses.

6. Batch manufacturing records

Manufacturing records must provide a complete account of the manufacturing history of each batch of a drug, showing that it has been manufactured, tested, and analyses in accordance with the manufacturing procedures and written instructions described, A separate batch manufacturing record should be prepared for each batch of drug produced, and should include the following information.

1) name and dosage form;
2) date of manufacture;
3) batch identification;
4) complete formulation of the batch;
5) the batch number (or analytical control number) of each component used in the formulation;

6) the actual yield obtained at different stages of manufacture of the batch with the theoretical yield;
7) a duly signed record of each followed, precautions taken, and special made throughout the manufacture of the batch;
8) a record of all in-process controls followed and of the results obtained;
9) a specimen of the actual coded label used;
10) identification of packaging materials, containers, and, where applicat used;
11) signature of the expert responsible for the manufacturing operations, an his signature;
12) an analytical report showing whether the batch complies with the specifications for the drug, date and duly signed by the responsible exper
13) a record of the decision regarding the release or rejection of the batch b control department; and
14) if the batch manufacturing records.

For reference purposes, all batch manufacturing records should be retained fo period.

Labelling and packaging

Labelling and packaging materials, including leaflets, should be stored a in such a way as to ensure that labels, packaging materials and leaflets different products do not become intermixed. Access to such material restricted to authorized personnel.[8]

Prior to packaging and labelling of a given batch of drug, the manuf control records specified should show that the batch has been duly tested, ap released by the responsible quality control expert. Prior to being issued, a containers, cartons, and boxes and all circulars, inserts, leaflet, etc., should and released as satisfactory for use by the designated person(s).

To prevent packaging and labelling errors a known number of labellin aging units should be issued and, if required, coded. Such issuance shou against a written, signed request that indicates the quantity and types required

Upon completion of the packaging and labelling operation, a comparis made between the number of labelling and packaging units issued and th items labelled and packaged plus the number of units not used. All coded should be destroyed. Any significant or unusual discrepancy in the numbe carefully investigated.

All finished drugs should be identified by labelling that should bear, clearly indicated, at least the following information:

1) the name of the drug;
2) a list of the active ingredients, showing the amount of each present, and a statement of the net contents, e.g., number of dosage units, weight or volume;
3) the batch number assigned by the manufacturer;
4) the expire date, if required;
5) *any* special storage conditions or handling precautions that may be necessary,
6) directions for use, and warnings and precautions that may be necessary; and
7) the name and address of the manufacturer or the person responsible for placing the drug on the market.

The quality control system

1. Quality control department

Every manufacturing establishment must have a quality control department supervised by a suitably qualified expert directly responsible to management but independent of other departments. They quality control department should control all starting materials, monitor the quality aspects of manufacturing operations, and control the quality and stability of drugs.[9]

The quality control department should have the following principal duties:

1) to prepare detailed instructions, in writing, for carrying out each test and analysis;
2) to release or reject each batch of starting materials;
3) to release or reject "half-finished" products, if necessary;
4) to release or reject packaging and labelling materials and the final containers in which drugs are to be placed;
5) to release or reject each batch of finished drug that is ready for distribution;
6) to evaluate the adequacy of the conditions under which starting materials, "half-finished" products, and finished drugs are stored;
7) to evaluate the quality and stability of finished drugs and, when necessary, of starting materials and "half-finished" products;
8) to establish expire dates and shelf-life specifications on the basis of stability tests related to storage conditions;
9) to establish, and when necessary revise, control procedures and specifications; and
10) to be responsible for the examination of returned drugs, to determine whether such drugs should be released, reprocessed, or destroyed. Adequate records of the disposition of such drugs should be maintained.

In order to fulfill its responsibilities, the quality control department should tak samples (e.g., of starting materials and finished drugs), according to established pro cedures. The samples should be properly labelled, and portion should be kept for futu reference.

The quality control department should maintained adequate analytical record concerning the examination of all samples taken. Such records should includes:

a) the result of every test performed, including observations and calculations, relating t compliance with the established specifications;
b) the source of the specifications used;
c) the signature(s) of the person(s) who performed the quality control procedures; and
d) a final review, the decision taken, and a dated endorsement by a duly authorize expert.

2. Quality control laboratory

The quality control department should have a laboratory available to it. Th laboratory should:

1) be adequately staffed and fully equipped for performing all quality control tests an analyses required during and after manufacture;
2) be supervised by a qualified expert.

Self-inspection

In order to maintain strict adherence to all manufacturing procedures and prescribe controls, it may be advisable for a firm to designate an expert or a team of experts t conduct regularly scheduled inspections of its overall manufacturing and contro operations. However, this should not be taken to mean that any firm that exercises sel inspection should be exempt from the official inspections required by the laws an regulations of the country in which it is located. Adequate records should be maintaine of the distribution of a finished batch of a drug in order to facilitate prompt and complet recall of the batch if necessary.

Complaints and reports of adverse reactions

Reports of injuries of adverse reactions resulting from the use of a drug should b forwarded to the appropriate authorities. Complaints regarding the quality of a drug including any change in its physical characteristics, must be thoroughly investigated. they prove well-founded, appropriate measures must be taken as soon as possible. Th measures taken should be recorded and filed with the original complaint.

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