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QUALITY CONTROL OF DRUGS

Report by the Director-General

1. In resolution WHA20.34, the Twentieth World Health Assembly requested that the Director-General undertake a number of measures for the purpose of assisting Member States in their efforts to improve the quality control of drugs. These measures are intended to be part of a comprehensive programme and consequently inter-related in various ways. Where appropriate they will be referred to in this report which is made in response to operative paragraph (iv) of the aforementioned resolution requesting the Director-General to report "on the principles which should be included in regulations under Article 21 of the Constitution of WHO, supplemented as may be necessary, by recommendations under Article 23, in regard to pharmaceutical products in international commerce and on the steps which the Organization would have to take to implement the programme of work involved to the Twenty-first World Health Assembly through the Executive Board with their comments".

2. In previous discussions by the Assembly and Board interest has been focused on three suggestions which, in the light of the aforementioned request by the Twentieth World Health Assembly, might be examined for their suitability of being embodied in such regulations or recommendations respectively. Those possibilities included:

(i) Certification by WHO that the drugs destined for exportation comply with established international standards of quality;

(ii) Certification by the government of the exporting country that any drug destined for exportation comply with standards of quality not less than those imposed for consumption in the country of origin;

(iii) Certification by the government of the exporting country that any drug destined for exportation has been produced in compliance with good manufacturing practices.

3. As regards suggestion 2.(i) it has been pointed out in previous discussions that a centralized certification of each consignment moving in international commerce would require a control machinery the personnel, technical, and financial resources of which would exceed by far the capacity of any international organism at this juncture.

4. The advisability and feasibility of suggestion 2.(ii) are likely to be jeopardized by two occurrences:

(a) The standards of the exporting country may be less strict than those of the country of importation.

(b) the impracticability for the exporting country of establishing a system of control which would have to be applied to each batch of each consignment in order to be reliable. Even if such certification was practicable its value would in any case depend upon the efficiency of the drug control system in the exporting country.

It will be realized that, the impact of such control measures is hampered by the fact that the legislation concerning quality control of drugs shows great variations from country to country. Little progress can therefore be expected until certain principles for pharmaceutical quality control will have been generally accepted and adhered to.

Notwithstanding the above-mentioned limitations, and in the spirit of suggestion 2.(ii), effect has been given to operative paragraph (v) of resolution WHA20.34 by means of a letter[1] requesting that Member States which export pharmaceuticals ensure that these are subject to control measures which will secure that they comply with standards of quality not less than those imposed on the domestic commerce of the exporting country.

5. In introducing international regulations along the lines of suggestion 2.(iii) advantage could be taken of what is now common practice in several countries, i.e., regular inspection under governmental authority of drug manufacturing plants, in accordance with established "requirements for good manufacturing practice".

6. Based on those already existing practices, the following provisions could be envisaged should Regulations be established under Article 21 of the Constitution:

A certificate would be issued, at the request of the importing country, by the manufacturer and endorsed by a national authority of the exporting country.

The manufacturer's certificate would contain:

a complete and pertinent statement of the quality specifications for that drug or pharmaceutical speciality;
a detailed description of the test methods employed for the determination of the conformity of the finished drug or pharmaceutical speciality with the specifications referred to above; and
additional data on packing materials, transport and storage conditions, expiry date if applicable, and conformity of labelling to requirements.

The endorsement of such certificates by the national control authority would be subject to fulfilment by the manufacturer of the following requirements:

the manufacturer adheres to "Requirements of Good Manufacturing Practices" - to be recommended under Article 23 of the Constitution - as witnessed by regular inspection of the plant by the national control authority;
the drug or pharmaceutical speciality complies with the quality specifications established for that drug or speciality, as witnessed by random sampling and testing performed by the national control authority.

7. As requested in operative paragraph (i) of resolution WHA20.34 "Requirements for Good Manufacturing Practice in the Production and Quality Control of Drugs and Pharmaceutical Specialities" (Annex) have been drafted by the Secretariat with the assistance of experts. Part A of the Annex describes briefly the general principles for quality control; part B deals with legislation and enforcement; and part C contains specified requirements for good manufacturing practice.

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[1] Reference C.L.25.1967 of 14 July 1967.

As is emphasized in part A of the Annex control at the production stage is imperative. The traditional attitude of relying only on the checking of the final product does not guarantee the production of consistently uniform batches of drugs and pharmaceutical specialities. It is, therefore, important that the quality is built in from the very beginning of manufacture and more and more countries are introducing legislation to this effect.

8. It is obvious that International regulations based on the recommended Requirements of Good Manufacturing Practice would serve the intended purpose only if and when enforced in an equal manner by all countries exporting drugs.

9. The availability of quality control certificates (as described in paragraph 6) for drugs in international commerce would not dispense the importing country from having, or having access to, control laboratories for random checking of the imported products, since there should be a final control to detect, for example, possible deterioration during transport and storage. The development of such national or regional laboratory facilities, referred to in operative paragraph (iii) of resolution WHA20.34, is determined by the availability of financial and human resources, as well as the administrative and legal pre-requisites. In this respect the Board will certainly note with interest that the projects of a national control institution in India and of a centralized quality control institution to serve the needs of several countries in Latin America are at an advanced stage of planning for presentation to UNDP. Similar projects are being pursued in Ceylon and Thailand on a bilateral basis in co-operation with Japan and the Federal Republic of Germany respectively.

10. A pre-requisite for the satisfactory performance of control at all levels is the availability of internationally recognized specifications for pharmaceutical quality control as well as of certain reference substances for the analytical work. Such specifications referred to in operative paragraph (ii) of resolution WHA20.34 are now available in their most recent version in the Second Edition of the International Pharmacopoeia. A system is being developed which will permit the publication at frequent intervals of up-to-date specifications on new drugs. International chemical reference substances needed for tests and assays laid down in these specifications are available from the WHO Centre for Chemical Reference Substances, Stockholm.

11. The financial implication referred to in operative paragraph (vi) of resolution WHA20.34 will depend on the course of action which the Board may wish to recommend to the Assembly.

DRAFT REQUIREMENTS FOR GOOD MANUFACTURING PRACTICE IN THE PRODUCTION AND QUALITY CONTROL OF DRUGS AND PHARMACEUTICAL SPECIALITIES

A. INTRODUCTION

1. Scope of quality control

The suitability of any drug or pharmaceutical speciality for its intended use, is determined by two groups of factors:

(a) efficacy weighed against safety to health according to label claim or as promoted or publicised and

(b) conformity to its specifications regarding identity, strength, purity and other physical characteristics.

Although these two groups of factors may be considered separately, they are, to some degree, interdependent.

Satisfactory levels of efficacy and safety can be achieved on the basis of assessment and evaluation of the drugs in respect of their pharmacology and toxicology, including their clinical evaluation. The desired quality of drugs and pharmaceutical specialities can be achieved by strict adherence to the specifications mentioned above. In fact, once the efficacy and safety have been established, the quality of drugs and pharmaceutical specialities available in commerce is judged by measuring identity, strength, purity and other relevant physical characteristics.

Quality control is practised to achieve sustained and uniform manufacture of products of desired quality levels. Therefore, this paper

will be limited to a basic discussion of quality control factors determining rejection or acceptance of drugs, pharmaceutical specialities and their components during or after manufacturing procedures. The essential factors in this respect are:

(a) product quality specifications and

(b) production control.

1.1 Product quality specifications

These are necessary to determine suitability for use in manufacture of starting materials, intermediates and half-finished products and to determine the quality of end products.

1.1.1 Starting material specifications

These may be found in official compendia, such as pharmacopoeias, codices and formularies.

If, for a certain substance, no official specifications are available, the purchaser will have to draw up a specification for his own use, or agree to the specifications proposed by the manufacturer of that substance.

Specifications for starting materials must be based on the characteristics of processes used for the production of these materials and will comprise:

(a) specific identification tests;

(b) purity tests;

(c) assay method;

(d) physical characteristics.

Other specifications may be added to facilitate use in manufacture.

1. 1.2. Specifications for intermediates and half-finished products

These specifications serve mainly production interests. They may be necessary to determine suitability of such products for further manufacturing operations or acceptability for the purchaser if such products are procured from outside sources.

1. 1.3. Specifications for finished (end) products

These are the established specifications for the finished drug and pharmaceutical speciality which must provide all acceptance criteria for these products in precise and detailed terminology enabling the designated control authority to determine their acceptability.

1. 2. Production control

It must be emphasised that quality cannot be tested into products but must be built in from the very beginning of manufacture. Therefore, production control is the chief tool in maintaining desired quality levels in intermediates, half-finished and finished products.

Starting materials, intermediates and half-finished products should be used in manufacturing only after their quality has been verified and found acceptable by testing, results of such testing being described in protocol.

Production control embodies the following principles:

1. 2.1. environmental control pertaining to suitability of premises, equipment and staff;

1. 2.2. manufacturing control with respect to (a) process-inherent factors which might adversely affect the execution of the manufacturing procedures and (b) adverse extraneous factors, such as contamination and mix-up of starting materials, intermediates, half-finished and finished products.

1. 2.3. final control of the finished products to assure that these comply with the established specifications and have been manufactured following the prescribed manufacturing procedures.

These principles are outlined in the section of this document pertaining to Good Manufacturing Practices (Part C).

B. LEGISLATIVE AND ENFORCEMENT ASPECTS

The following may be of interest to countries considering the adoption of legislation with regard to quality control of drugs and pharmaceutical specialities.

If legislative measures pertaining to quality control of drugs and pharmaceutical specialities are adopted, the need for an adequate law enforcement system is self-evident. It is essential to enforce Good Manufacturing Practices to ensure delivery of quality products to the consumer. Furthermore, it is obvious that these legislative measures will encourage the build-up of quality control of drugs entering into international commerce, since the Good Manufacturing Practices must be enforced primarily in the country of origin.

In this connexion a reference must be made to the report of a WHO European Technical Meeting in Warsaw 1961[1] in which the organization of a National Control Authority was discussed, including administrative, inspection and laboratory services.

C. GOOD MANUFACTURING PRACTICES

1. GENERAL CONSIDERATIONS

In the pharmaceutical industry the overall control of drugs is essential to assure that the individual consumer receives drugs and pharmaceutical specialities of high quality.

The same overall control is also of major importance for the manufacturer. There is no room for haphazard operations where one is dealing with life-saving and life-preserving products.

Certainly, difficulties will arise in establishing the necessary criteria under which, in our present day, drugs and pharmaceutical specialities can be manufactured, to assure that the manufactured drug can be used with confidence in that it will achieve the desired effect.

This text develops a set of Good Manufacturing Practices that delineate basic and essential principles necessary in the manufacture of drugs and pharmaceutical specialities of desired quality. Such principles should contribute substantially to the consistency of manufacturing procedures and operations, complementing the various control tests followed from the very

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[1] Wld Hlth Org. techn Rep. Ser. 1962, 249, 26.

beginning to the very end of the entire manufacturing cycle. Adherence to the recommended practices will contribute substantially to the manufacture and output of consistently uniform batches of drugs and pharmaceutical specialities possessing high quality.

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

The Good Manufacturing Practices outlined in this text should be considered as general directives which, whenever necessary, may be suited to individual needs, provided the desired and established standards of drug quality are still achieved.[1]

2. GLOSSARY

2. 1. Drug

A drug is any substance or mixture of substances manufactured, sold, offered for sale or represented for use in:

2. 1.1. treatment, mitigation, prevention or diagnosis of disease, abnormal physical state or the symptoms thereof in man or animal;

2. 1.2. restoring, correcting or modifying organic functions in man or animal.

2. 2. Pharmaceutical speciality

A pharmaceutical speciality is a simple or compound drug ready for use and placed on the market under a special name or in a characteristic form.

2. 3. Manufacturing

Manufacturing consists of all operations in the production of a drug or a pharmaceutical speciality. Such operations include one or more of the following:

processing, compounding, formulating, filling, packaging, labelling, etc.

2. 4. Starting materials (and components)

Starting materials (and components) include all substances whether active or inactive or whether they remain unchanged or become altered, that are employed in the manufacture of drugs and pharmaceutical specialities.

2. 5. Batch[2]

A batch is a portion of any drug or pharmaceutical speciality produced during

the same cycle of manufacture. The essence of a manufacturing batch is its homogeneity.

2.6. Batch number

A batch is identified by a conventional sign shown in the labelling of the drug or pharmaceutical speciality which permits complete identification of the production history of that batch and thereby enabling a quick trace-back and review of all stages of manufacture and control.

2.7. Quarantine

Status of material isolated and not available for use until released by a designated responsible expert.

2.8. Quality Control

Quality control is each and every measure, specifically designed to achieve uniform and assured output of batches of drugs and pharmaceutical specialities conforming to established specifications of identity, strength, purity and other physical characteristics.

2.9. Intermediate

Any substance or mixture of substances intended for further alteration in subsequent steps of manufacture.

2.10. Half-finished material

Any drug which must undergo further manufacture.

2.11. Active ingredient

A substance which is intended to give the desired effect of the finished drug or pharmaceutical speciality.

2.12. Inactive ingredients

Substances that are used in preparing a drug or pharmaceutical speciality but which are to be considered as excipients. These would include preservatives, buffers, diluents, fillers, solubilizers, vehicles, anti-oxidants, colouring and flavouring agents, etc.

2.13. Purity

The term purity, as used in this text, signifies the limits of presence, in any substance, of other chemical or biological entities.

3. PERSONNEL

3. 1. Experts responsible for the supervision of the manufacture and control of drugs and pharmaceutical specialities should:

3. 1.1. possess the qualifications of scientific education and practical experience required by national legislation;

3. 1.2. preferably not have any interests outside the manufacturer's organization that prohibits or restricts devoting the necessary time to their assigned responsibilities and/or that may be considered a conflict of financial interest;

3. 1.3. be given full authority and facilities necessary to accomplish their mission effectively.

3. 2. In addition to the personnel already referred to, an adequate number of technically trained persons should be available to carry out the manufacturing and controlling operations in accordance with the established procedures and specifications.

Note:

a) The scientific education of experts, responsible for supervision of manufacture and control operations should include the study of an appropriate combination of the following scientific disciplines:-

- chemistry (analytical chemistry, biochemistry, physical chemistry, etc.)
- chemical engineering
- microbiology
- pharmaceutical sciences and technology
- pharmacology and toxicology
- physiology and histology
- other related sciences.

b) Experts in key positions should have adequate practical experience in the manufacture and control of drugs or pharmaceutical specialities. In order to gain such experience, a preparatory period may be required. During this period, the expert should exercise his duties under professional guidance.

c) The scientific education and practical experience of experts should be such as to enable them to exercise independent professional judgment, based on application of scientific principles and understanding to the practical problems they encounter in manufacture and control of drugs and pharmaceutical specialities.

4. PREMISES

4. 1. Premises in which drugs are manufactured, processed, packaged, labelled or stored shall:

4. 1.1. not be utilised for any other purpose;

4. 1.2. be well lighted and ventilated, and if necessary heated and air conditioned;

4. 1.3. provide adequate working space as well as adequate room for the orderly placement of equipment and materials to minimize or eliminate any risk of mix-ups between different drugs and their components, and to control the possibility of cross-contamination by another drug that is manufactured, processed, packaged, labelled or held on the same premises.

4. 2. Highly toxic drugs should be stored in special rooms provided for this purpose, and be subjected to limited access of personnel.

4. 3. For special purposes, such as the manufacturing of drugs that can be sterilized in their final and immediate containers, separate enclosed areas must be provided. These areas should be essentially dust-free, preferably supplied with filtered air at a pressure higher than that in adjacent areas, and be subjected to limited access of personnel.

4. 4. For manufacturing of drugs that cannot be terminally sterilized a separate and enclosed area specifically designed for this purpose should be used.

4. 5. The areas mentioned under 4.3. and 4.4. should be checked routinely against established standards by performing microbial counts of the air in the area during manufacturing operations. Adequate records of performed checks of these areas should be available.

5. EQUIPMENT

5. 1. Manufacturing equipment should be designed and maintained in such a way as:

5. 1.1. to be suitable for its intended use;

5. 1.2. to permit easy and thorough cleaning;

5. 1.3. to exclude any contamination of drugs and their containers during their manufacture.

5. 2. Manufacturing equipment and utensils should be cleaned and if necessary sterilized, and kept in accordance with written and specific directions. Adequate records of such operations should be kept.

5. 3. In addition, the suitability of the equipment used for aseptic filling should be proven at pertinent intervals. This may be done by testing the filling equipment by microbiological methods. Adequate records of such tests should be kept.

6. SANITATION

6. 1. Manufacturing premises should be clean, sanitary, orderly and free from accumulated waste, debris, vermin and pets.

6. 2. A written sanitation programme should be available, indicating:

6. 2.1. specific areas to be cleaned, and cleaning intervals;

6. 2.2. cleaning procedures to be followed and, if necessary, equipment and materials to be used for cleaning;

6. 2.3. personnel assigned to and responsible for cleaning operations.

6. 3. No eating, smoking or any unhygienic practice shall be permitted in manufacturing areas.

6. 4. Manufacturing personnel should have a sufficient number of clean, well-aired toilet facilities and rooms with adequate facilities for washing, and changing

clothes near working areas at their disposal.

7. STARTING MATERIAL

7. 1. All starting materials to be used at any stage in the manufacture of drugs and pharmaceutical specialities must be:

7. 1.1. identified and visually examined for damage of container;

7. 1.2. inventoried, and recorded as to their origin, date of receipt, date of analysis and release by quality control department and their subsequent use in manufacture;

7. 1.3. properly stored;

7. 1.4. specifically marked as undergoing testing, and/or if possible quarantined for eventual release by the quality control department;

7. 1.5. properly sampled by quality control representatives;

7. 1.6. tested for compliance with required specifications;

7. 1.7. released by quality control through written instructions;

7. 1.8. properly and conspicuously relabelled as accepted or approved and subsequently transferred if necessary, to areas designated for storage of approved material.

7. 2. All rejected starting materials should be conspicuously identified as such. These materials should be destroyed or returned to the supplier as soon as possible.

8. MANUFACTURING CONTROLS AND DIRECTIONS

8. 1. Cleanliness

Apparatus, equipment and materials used in manufacturing shall be thoroughly clean and, whenever necessary, sterile and free of all contaminants. When indicated, all equipment should be disassembled, if possible, and thoroughly cleaned to preclude the carry-over of drug residues from previous batches produced with the same apparatus or equipment.

8. 2. Manufacturing equipment and containers

All equipment, vessels, and containers used in the manufacturing process, regardless of the stage of manufacture, must be identified by securely attached labels bearing the name and/or identification number for the processed material.

8. 3. Precautions against contamination

8. 3.1. All manufacturing operations should be confined to separate areas intended for such purposes, with complete equipment used exclusively in those areas, or provisions should be made to assure that no extraneous contamination or mixup occur.

8. 3.2. Sterile operations must be performed in specially designed and constructed areas for their intended purpose, as indicated under "Premises", section 4.3., 4.4. and 4.5.

8. 3.3. All operations in which highly potent drugs, including antibiotics, are weighed, mixed, micronized, formulated, filled, encapsulated, tabletted, etc.,

should be conducted in confined areas, with adequate exhaust systems or areas under negative pressure to preclude drug to drug migration. The exhaust air from these areas should be specially treated to remove dust and drug contaminants from those areas.

8. 4. Manufacturing personnel

8. 4.1. No person known to be affected with a disease in a communicable form or to be the carrier of such a disease, and no person with open lesions on the exposed surface of the body, should be engaged in the manufacture of drugs and pharmaceutical specialities. Manufacturing personnel should undergo periodic health checks.

8. 4.2. In manufacturing areas clean working garments should be worn over, or in place of, street clothing.

8. 4.3. Personnel engaged in sterile operations must wear clean and sterilized gowns, caps, masks, gloves and overshoes. They must also wash and rinse their hands with a suitable and harmless disinfectant prior to dressing and entering sterile areas.

8. 4.4. Whenever necessary, manufacturing personnel must wear protective clothing, shoes, headgear, dust masks, etc., and this protective clothing should remain in the area. In some instances, it may be necessary to restrict personnel to their respective and immediate working areas.

8. 5. Manufacturing procedures and written instructions (Master Formula)

8. 5.1. Manufacturing procedures and written instructions must be prepared under direct supervision and endorsement of responsible experts, as indicated in section 3, possessing the necessary authority.

8. 5.2. These procedures and written instructions should contain at least the following data:

8. 5.2.1. Name and presentation of the drug or pharmaceutical speciality;

8. 5.2.2. Description or identification of the final and immediate container(s) and, where applicable, of the closures to be used;

8. 5.2.3. Identity, quantity and quality of each starting material to be used, irrespective of whether it appears or not in the finished drug or pharmaceutical speciality. Permitted overages to be included in the formulated batch should be indicated as such herein;

8. 5.2.4. Theoretical yield to be expected from the formulation;

8. 5.2.5. Detailed instructions and, when necessary, precautions for manufacture and storage of the drug or pharmaceutical speciality, as well as intermediates, and half-finished materials;

8. 5.2.6. All necessary quality control tests and analyses to be carried out during each and every stage of manufacture.

8. 6. Batch manufacturing records

8. 6.1. Manufacturing records must reflect a complete and pertinent account of the manufacturing history of each batch. A separate batch manufacturing record shall be prepared for each batch of drug and pharmaceutical speciality produced. This record must include the following information:

8. 6.1.1. Name and presentation of the drug or pharmaceutical speciality;

8. 6.1.2. Date of manufacture;

8. 6.1.3. Batch identification;

8. 6.1.4. Complete formulation of the batch, as referred to sub 8.5.2.3;

8. 6.1.5. The batch number (or analytical control number) of each component used in the formulation;

8. 6.1.6. Actual yield obtained at pertinent stages of manufacture of the batch;

8. 6.1.7. A duly signed record of each step followed, precautions taken and special observations made during the entire manufacturing cycle of the batch;

8. 6.1.8. All in-process controls followed and results obtained;

8. 6.1.9. Specimen of the actual coded labelling used;

8. 6.1.10. Identification of packaging materials, containers and, where applicable, of closures used;

8. 6.1.11. Date and signature of the expert responsible for the manufacturing operations;

8. 6.1.12. Full analytical report showing whether the batch complies with the prescribed specifications for that drug or pharmaceutical speciality; this report should be duly signed and dated, and endorsed by the expert responsible for quality control, to permit the batch to be released.

8. 7. Maintenance of records and samples

8. 7.1. During an appropriate period all manufacturing and control records of a batch should be preserved for future reference.

8. 7.2. A sufficient number of representative samples of each batch should also be kept for future testing as required.

9. LABELLING AND PACKAGING

9. 1. Labelling and packaging materials including leaflets, shall be adequately and separately stored to eliminate any risk of mix-ups. Access to these materials shall be restricted to authorised personnel.

9. 2. Prior to packaging and labelling of a particular batch of a drug or pharmaceutical speciality, records should show that the batch has been duly tested, approved and released by the responsible quality control expert. Prior to being issued, all labelling (immediate or container labels, carton or box labels, circular inserts or leaflets, etc.) should be reviewed, examined and released as satisfactory for use by the designated authority.

9. 3. To prevent packaging and labelling errors, an accurately known number of labels should be issued and properly coded. Upon completion of the packaging and labelling operation, a careful check should follow to determine the actual number of labels used against the number issued and coded. This check should include both destroyed and unused labels.

9. 4. All finished drugs and pharmaceutical specialities should be identified by appropriate labelling. This labelling should bear clearly at least the following:-

9. 4.1. Name of the drug or pharmaceutical speciality;

9. 4.2. Quantitative declaration of the active ingredients and net contents;

9. 4.3. The batch number assigned by the manufacturer;

9. 4.4. The expiry date, if any;

9. 4.5. Name and location of the manufacturer;

9. 4.6. Any special storage or handling precaution if necessary;

9. 4.7. Any other indications or directions required to accompany the packaged drug.

10. QUALITY CONTROL SYSTEM

10. 1. A quality control system involving the control of all starting materials, control and supervision of manufacturing operations, quality control of drugs and pharmaceutical specialities and control of their stability should exist in every pharmaceutical manufacturing establishment.

10. 2. A quality control laboratory must be available and should:

10. 2.1. be adequately staffed and fully equipped for performing all quality control tests and analyses required during and after manufacture;[1]

10. 2.2. be supervised by a qualified expert as referred to in Section 3, who should be directly responsible to management;

10. 2.3. receive prompt information on all changes and modifications in the manufacturing procedures and written instructions as referred to in Section 8.5.

10. 3. The quality control department should have the following principal duties :

10. 3.1. The establishment of detailed and pertinent written procedures for carrying out each test and analysis.

10. 3.2. The control and release of each batch of starting material;

10. 3.3. The control and release of intermediate products, if necessary;

10. 3.4. The control and release of each batch of finished drug or pharmaceutical speciality ready and held for distribution;

10. 3.5. The control and release of the immediate containers in which the drug will be filled;

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[1] Animal quarters, if required, and the care of animals should be adequate (Wld Hlth Org. techn Rep. Ser. 1966, 323, par. 2,5 p.14 and 3,5 p.16)

10. 3.6. The control of the adequacy of the conditions for the storage of starting materials, intermediates and finished drugs and pharmaceutical specialities;

10. 3.7. Evaluation of the quality and stability of finished drugs or pharmaceutical specialities, and whenever necessary of starting materials and intermediates;

10. 3.8. The proposal or establishment of expiry dates and shelf-life whenever necessary.

10. 3.9. The proposal or establishment and necessary revision of current control procedures and specifications.

10. 4. In order to comply with its quality control responsibilities, the control department shall take samples in sufficient quantities according to the established procedures and keep appropriate analytical records. These samples must be properly labelled. The laboratory control records as well as the samples should be preserved for future reference. (See 8.7.)

10. 5. The quality control department shall keep pertinent records concerning the control of each batch of drugs and pharmaceutical specialities manufactured. These signed records should include:

10. 5.1. A final evaluation of the product and a decision as to whether the analysed and controlled batch does or does not conform to the established specifications.

10. 5.2. The source of the specifications used.

10. 5.3. Signatures of the person or persons who have performed the controls.

10. 5.4. A final review and dated endorsement by a duly authorized expert.

11. SELF-INSPECTION

For the purpose of ascertaining strict adherence to all manufacturing procedures and prescribed controls to be followed, it may be advisable to designate some responsible expert or a team of experts to conduct regularly scheduled inspections of the overall manufacturing and control operations of the firm. This however, should not be misinterpreted in that any firm, electing to exercise self-inspection, should be exempt from the official inspections required by national laws and regulations of the country in which that firm is located.

12. DISTRIBUTION RECORDS

Adequate records shall be maintained regarding the distribution of the finished batch of the drug or pharmaceutical speciality in order to facilitate prompt, complete, and effective recall of the batch if necessary.

13. COMPLAINTS AND REPORTS OF INJURIES

All written consumer and other complaints and reports of injuries from use of a drug or a pharmaceutical speciality, must be thoroughly investigated. If they prove well-founded appropriate measures must be taken as soon as possible. The relevant measures should be recorded separately and filed with the original complaint or reported injury.