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**WHO EXPERT COMMITTEE
ON SPECIFICATIONS FOR
PHARMACEUTICAL
PREPARATIONS**

Twenty-second Report

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**WHO EXPERT COMMITTEE ON SPECIFICATIONS
FOR PHARMACEUTICAL PREPARATIONS**

Geneva, 14-19 October 1968

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WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS *

Twenty-second Report

The WHO Expert Committee on Specifications for Pharmaceutical Preparations met in Geneva from 14 to 19 October 1968. Dr P. Dorolle, Deputy Director-General, opened the meeting on behalf of the Director-General. Dr T. Canbäck was elected Chairman and Professor M. A. Attisso Vice-Chairman. Mr C. A. Johnson and Mr R. J. Samson were appointed Rapporteurs.

1. QUALITY CONTROL OF DRUGS

In 1967,¹ the Twentieth World Health Assembly requested the Director-General to take a number of measures to assist Member States in their efforts to improve the quality control of drugs. In particular, it called for the formulation, as soon as possible, of principles for quality control procedures that should be applied to drug manufacturing practice. A draft document incorporating such principles, accompanied by a number of recommendations concerning factors to be considered in maintaining good manufacturing practices, was subsequently submitted to the Twenty-first World Health Assembly under the title "Draft Requirements for Good Manufacturing Practice in the Manufacture and Quality Control of Drugs and Pharmaceutical Specialities", and was favourably received. The draft had also been sent to Member States with the purpose of obtaining comments. The response indicated that no substantial changes were necessary,

* Earlier WHO Expert Committees that produced reports on this subject were known as "WHO Expert Committee on the Unification of Pharmacopoeias" (1st to 7th reports) and subsequently as "WHO Expert Committee on the International Pharmacopoeia" (8th and 9th reports). The 10th to 20th reports, using the present title, were issued in mimeographed form only. The 21st report was published as *Wld Hlth Org. techn. Rep. Ser.*, 1965, No. 307.

¹ Resolution WHA 20.34, *Off. Rec. Wld Hlth Org.*, No. 160, p. 19.

although certain points of detail needed further clarification. The comments were reviewed and the revised draft was adopted, with minor amendments, by the Committee. The final text is reproduced in Annex 2; some principles on which quality control should be based are discussed in Annex 1.

2. DETERMINATION OF MORPHINE IN OPIUM

2.1 Present status

The Committee reviewed the progress of work to date on this project. Collaborative tests on the modified Mannich method of the Austrian Pharmacopoeia IX proved disappointing and further work, based on the recommendations of Schultz & Schneckenburger,¹ was undertaken. Much better results have been obtained by this modification of the method, although they are still too variable to permit unqualified recommendation of the technique. The Schultz & Schneckenburger method involves the use of an alumina column, and variation in the quality of alumina used is believed to contribute to the variability of the results. A source of supply of specially standardized alumina has been arranged and a third round of collaborative tests has been undertaken. An alternative method of extraction and purification prior to precipitation of the morphine, based on a partition chromatographic method described by Smith, Levine & Banes,² was also tested. Results obtained by the Schultz & Schneckenburger method were substantially higher than those given by the partition chromatographic method, and the coefficient of variation was lower. The morphine dinitrophenylether produced by the Schultz & Schneckenburger method was slightly more contaminated with small quantities of impurities than was that produced by the chromatographic method, but the extra contamination was by no means sufficient to account for the higher results obtained. It is felt that the results given by the Schultz & Schneckenburger method are not only more precise, but also more realistic, and the Committee agreed to continue work on the procedure.

2.2 Future work

The Schultz & Schneckenburger method will undergo detailed study in a single laboratory in order to discover factors that might contribute to the variability of results.

Confidence in the proposed Schultz & Schneckenburger assay method would be greatly increased if it were found to give, for a given sample of opium, results that showed satisfactory correlation with the actual factory

¹ *Arch. Pharm. (Weinheim)*, 1965, **298**, 548.

² *J. Ass. off. agric. Chem.*, 1968, **51**, 180.

yields of morphine from the same sample. The necessary data might be obtained by direct inquiries addressed to leading processors. In addition, it would be extremely useful if the processors were willing to furnish similar figures correlating actual factory yields of morphine with those theoretically expected on the basis of results obtained by their routine assay method. However, this project may well be delayed until the new study of the variables involved in the Schultz & Schneckenburger method is completed. If modifications of the technique are found to be desirable, details could then be furnished to the opium processing factories.

The Committee decided to seek the co-operation of a few official opium test laboratories in assaying, by means of their normal routine methods, the five opium samples used in the collaborative study referred to above. The results could then be compared with those obtained in the collaborative study.

3. PROPOSED SPECIFICATIONS FOR ANTITUBERCULOSIS DRUGS

The Committee began work on certain specifications for antituberculosis drugs that are not included in the second edition of the *International Pharmacopoeia*¹ but that are widely used in UNICEF/WHO-assisted field projects.

Draft specifications prepared by the State Institute for the Control of Drugs, Prague, in the style of the *International Pharmacopoeia*, and on the basis of published data and information supplied by manufacturers, were examined by the Committee after they had been reviewed, verified, and commented on.

3.1 Calcium benzamidosalicylate, pyrazinamide, and ethionamide

The Committee accepted, subject to the making of minor changes in the text of the specifications, the proposed monographs on calcium benzamidosalicylate and pyrazinamide. The monograph submitted on ethionamide will be completed by including a description of a thin-layer chromatographic method for the detection of possible impurities.

3.2 Thioacetazone, thioacetazone tablets, and thioacetazone and isoniazid tablets

The Committee asked the Secretariat to ascertain the principal types of impurities that may be found in thioacetazone, thioacetazone tablets,

¹ World Health Organization (1967) *Specifications for the quality control of pharmaceutical preparations*—second edition of the *International Pharmacopoeia*, Geneva.

and thioacetazone and isoniazid tablets. Depending on the information received, an appropriate method for the detection of impurities will be established.

3.3 Ion-exchange chromatography

Since assay of the substances noted above involves the use of ion-exchange chromatographic techniques, a description of such techniques was examined and accepted.

3.4 Further work

The Committee decided that priority should be given to the establishment of specifications for the following antituberculosis preparations: ethambutol, isoniazid and para-aminosalicylic acid tablets, and calcium benzamidosalicylate and isoniazid tablets.

4. INTERNATIONAL CHEMICAL REFERENCE SUBSTANCES

4.1 Evaluation and use

The Committee considered the general factors that should be taken into account in the evaluation and use of international chemical reference substances. One such factor is the complications arising from polymorphism; for example, the infrared spectrum of a given chemical reference substance may differ from that of the residue obtained by evaporating an extract of a dosage form of the drug. It may be possible to circumvent this problem by the use of solution spectra.

In order to assess the extent to which contaminants may interfere with an assay, the Committee considered that, whenever applicable, the technique used to assay a drug and its dosage forms should be used as an additional means for detecting contaminant spots on thin-layer chromatograms of international chemical reference substances. For example, it would be useful to employ blue tetrazolium to detect contaminants on corticosteroid chromatograms, and ultraviolet absorbance as a means for detecting contaminants on thin-layer chromatograms of the semisynthetic penicillins. When a reference substance is used for comparison in an ultraviolet absorption assay, a small amount of a contaminant that is highly absorbing at the wavelength concerned can significantly affect the accuracy of the determination.

Consideration should also be given to the possibility of assessing such interference (1) by comparing the absorptivity of the reference substance with that of the material that remains in the solid phase during a phase

solubility determination, and (2) by comparing the absorptivity of the reference substance with that of a sample whose content of impurities has been increased by recrystallization from mother liquors.

The results of phase solubility analysis should be expressed on a statistical basis, giving an estimate of total impurities and the probable limits. It has been recommended that estimates obtained by phase solubility assay be supported by other methods for assessing the suitability of a given reference substance for its intended use. In the opinion of the Committee, such supporting methods have not yet been sufficiently developed to make possible a thorough evaluation of samples, and further attention should be given to the development of thermo-analytical and quantitative chromatographic techniques for this purpose. Occluded solvents should also be sought for by techniques such as gas chromatography and, where feasible, nuclear magnetic resonance. The purity of compounds should also be determined by assays of functional groups where appropriate methods are available.

It is desirable that a collaborative study be undertaken to determine the degree of reliability of results given by phase solubility techniques.

4.2 Establishment of reference substances

After examination of the relevant documents, the Committee recommended the establishment of the following reference substances for the purposes noted in the second edition of the *International Pharmacopoeia*:¹

Ampicillin	Hydrocortisone
Ampicillin sodium	Hydrocortisone acetate
Ampicillin trihydrate	Lanatoside C
Chloramphenicol	Methyltestosterone
Cloxacillin sodium	Meticillin sodium
Cortisone acetate	Nafcillin sodium
Deoxycortone acetate	Ouabain
Dexamethasone	Oxacillin sodium
Digitoxin	Pheneticillin potassium
Digoxin	Prednisolone
Ergometrine maleate	Prednisolone acetate
Ergotamine tartrate	Prednisone
Estradiol benzoate	Progesterone
Ethinylestradiol	Propicillin potassium
Ethisterone	Riboflavin
Folic acid	Testosterone propionate
Griseofulvin	Warfarin

¹ World Health Organization (1967) *Specifications for the quality control of pharmaceutical preparations*—second edition of the *International Pharmacopoeia*, Geneva, p. 712.

4.2.1 *Prednisolone*

The Committee noted that prednisolone was the least pure of the steroids examined. However, it had proved impossible to obtain material of a better quality and, since the lack of an international standard might cause many difficulties, the Committee considered the inclusion of prednisolone in the list of reference substances to be justifiable, provided the exact amount of impurities present was known. As soon as a sample of better quality becomes available, the existing sample will be replaced.

4.2.2 *Nafcillin sodium*

It was noted that the water content of nafcillin sodium had been reported in terms of loss of weight on drying, whereas the *International Pharmacopoeia* specifies that its water content should not exceed 2% as determined by the Karl Fischer method. These two methods of determining water content give different results, although the difference appears to be constant. Consequently, it is important that the same method be used when performing comparative assays of different samples of nafcillin sodium. It was suggested that Karl Fischer reagent might react with nafcillin and that this problem be investigated. Depending on the findings of this investigation, it might be necessary to revise the monograph in the *International Pharmacopoeia*.

4.2.3 *Warfarin*

The Committee noted that the monograph on Warfarin Sodium in the *International Pharmacopoeia* is in urgent need of revision.

4.3 Future work

A number of requests for the establishment of chemical reference substances were received.

The Committee decided that work should begin on the preparation of chemical reference substances for phenoxymethylpenicillin and benzylpenicillin. It was also agreed that work be continued on reference substances for the semisynthetic penicillins.

It was further recommended that a review of the work that would be necessary to prepare the following reference substances should be carried out by the WHO International Reference Centre for Chemical Reference Substances : benzathine penicillin, cephaeline hydrochloride, emetine hydrochloride, ergosterol, gitoxin, kebuzone, sennoside A, and sennoside B.

The Committee noted that some melting-point reference substances will shortly need replacement; and considered this will provide an opportunity to review the substances that are included in the present collection.

The Committee requested that, for future discussion, a statement be prepared of the principles that should guide policy on the establishment of chemical reference substances.

In the opinion of the Committee, the need for chemical reference substances will increase in the future, as a result of the introduction of new drugs in world commerce and of the wider use of comparative analytical techniques. Consequently, a greater co-operative effort on the part of organizations that prepare reference substances would be desirable, and the co-operation of regional and national pharmacopoeial authorities should be sought. One of the principal objectives should be to avoid the establishment of many different reference substances for the same material. WHO could play an important role in co-ordinating such an undertaking, and the Committee recommended that, as a first step, WHO conduct a survey of its Member States to obtain full information on work they may be carrying out on chemical reference substances for pharmaceutical quality control.

5. PROPOSALS FOR THE EARLY PROVISION OF DRUG SPECIFICATIONS

5.1 General considerations

In certain countries with a highly developed pharmaceutical industry and legislative system, there is close governmental control of the manufacture and distribution of drugs. Such control contributes substantially to ensuring that a patient receives a drug as prescribed by the physician and that it is of the requisite quality (i.e., that it has been properly manufactured and tested). The extent to which a national health authority will be able to determine the adequacy of the quality of drugs will vary according to the facilities and expertise that are available.

The need for assisting Member States to achieve adequate quality control of drugs, whether imported or locally produced, has been expressed in several resolutions of past World Health Assemblies.

Of particular significance is resolution WHA20.34,¹ which requested the Director-General "to continue work on analytical control specifications for international acceptance to be published as they are completed". The wording of the resolution bears witness to the urgency that the World Health Assembly attaches to the dissemination, as rapidly as possible, of drug specifications.

The present procedure of publishing the *International Pharmacopoeia* as a bound volume involves substantial delays in the dissemination of

¹ *Off. Rec. Wld Hlth Org.*, No. 160, p. 19.

specifications on drugs. An alternative procedure, in which WHO would solicit, review, and collate reference data on the quality control of new drugs, and distribute them in the form of information sheets, has been under discussion for a number of years.¹ Such information, if available early, would be of immediate use to official control laboratories. It may reasonably be assumed that laboratories using such reference data would, on the basis of their practical experience, submit comments and suggestions which could be used in revising the original data sheets, with a view to eventual inclusion in the *International Pharmacopoeia*. This scheme would obviously require close and continuous co-operation between national control authorities, the pharmaceutical industry, and WHO. Such co-operation should contribute substantially to the wider acceptance of uniform specifications.

The Committee recognized that the success of a scheme such as that proposed below, would depend on the willingness of manufacturers to disclose quality control factors that would permit acceptance or rejection of their products. The correct evaluation of such factors, which could be included in a provisional monograph to be published when completed, would necessitate the disclosure of sufficient background information on the chemical and physical properties of drugs as determined by analytical techniques, often of a highly advanced nature. Such information would be obtained by means of a questionnaire (see Annex 3). Since the information requested might well include data considered by the manufacturer to be confidential, the Organization would undertake, if requested, to restrict its dissemination to experts actively engaged, on behalf of the Organization, in reviewing the provisional monographs that would be requested to accompany the completed questionnaire.

The Committee feels that, in the preparation of monographs, the fullest attention must be paid to modern techniques of analysis that are now used in the more advanced manufacturing control laboratories. It realizes that the modification of such methods so as to make them suitable for description in a standard monograph involves difficulties, and urges that priority be given to overcoming such problems.

5.2 A scheme for the early provision of drug specifications

In the first phase of the scheme, WHO would monitor journals, official publications, etc. for information on the marketing of new drugs. The questionnaire (see Annex 3) would then be sent to the manufacturers concerned seeking information about the drugs. It is hoped that ultimately such close co-operation could be achieved that those who introduce new drugs into international commerce, or national commerce with the inten-

¹ See, e.g., *Wld Hlth Org. techn. Rep. Ser.*, 1957, No. 138.

tion of extending the distribution to international markets later, would take the initiative in supplying WHO with information.

The Committee considered that it would be advisable for the manufacturer to supply, together with the completed questionnaire and adequate samples of the drug, a draft provisional monograph.

After receiving the completed questionnaire, samples of the drug concerned, and a draft provisional monograph, WHO would submit them to a suitably chosen group of experts. The experts would evaluate the suitability of the draft provisional monograph proposed by the manufacturer against the background of the analytical data supplied. On the basis of their report the draft would either be approved (and promptly issued as a provisional monograph) or returned to the manufacturer with proposals for amendments. The manufacturer's comments on the proposals would be submitted to WHO within a specified period and reviewed by the group of experts; subject to their approval, with any necessary amendments, the approved provisional monograph would then be issued as soon as practicable.

After formal acceptance, WHO would distribute the provisional monograph, accompanied by the extensive analytical background data (with the exception of those considered to be confidential), without delay to Member States, making it clear that, in the opinion of the Secretariat, the monograph constituted a sufficient basis for the acceptance or rejection of the drug in question.

It is believed that the procedure outlined above would make it possible for provisional monographs on new drugs to be made available quickly, perhaps within a year, to those with official responsibility for determining whether drugs introduced into their countries comply with acceptable standards.

In the event that a manufacturer did not supply a draft monograph with the completed questionnaire, WHO would prepare such a draft from the information provided.

If such a scheme were adopted, the fact that WHO requested information and a draft monograph on a given drug would not constitute assurance that a monograph on the drug and its dosage forms would ultimately be included in the *International Pharmacopoeia* or any national pharmacopoeia.

The Committee recommend that the above proposal be given further study in order to implement the second operative paragraph of resolution WHA20.34.

6. RADIOACTIVE PHARMACEUTICALS

The Committee recommended that WHO expand its work on the preparation of specifications for radioactive pharmaceutical products. They noted that, although WHO is responsible for preparing such specifications,

it collaborates when necessary with the International Atomic Energy Agency on certain technical matters.

7. MICROBIAL CONTAMINATION OF NONSTERILE DRUGS

During the past few years there has been growing concern with excessive and undesirable microbial contamination of nonsterile drugs and adjuvants, and the Committee recommended that this problem be given close attention by WHO.

ACKNOWLEDGEMENTS

The Committee extends its thanks to the following for the valuable assistance they have given : Dr J. J. DiLorenzo, Food and Drug Administration, USA, Dr M. A. Kluyev, State Inspection for Quality Control of Pharmaceuticals and Medical Tools, USSR, and Dr E. Lang, Ciba Ltd., Basle, Switzerland, for their contribution to the preparation of Annexes 1 and 2 ; Mr A. Arzamascev, Pharmacopoeia Commission of the USSR, and Dr L. Chafetz, Warner-Lambert Research Institute, Morris Plains, N.J., USA, for reviewing proposed international chemical reference substances ; and Dr F. C. Nachod, Sterling-Winthrop Research Institute, Rensselaer, N.Y., USA, for preparing a proposed description of ion-exchange chromatographic procedures.

Annex 1**PRINCIPLES OF PHARMACEUTICAL QUALITY CONTROL**

The suitability of drugs for their intended use is determined by

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

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

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

In order to ensure that all batches of a given drug are equally efficacious and safe, it is essential to establish adequate specifications for the drug and its dosage forms. The desired quality can then be achieved by strict adherence to these specifications. In fact, once their efficacy and safety have been established, the quality of drugs available in commerce is judged by identifying them and by determining their strength, purity, and other characteristics.

The aim of quality control is to achieve sustained and uniform manufacture of products of defined quality. Consequently, the following discussion is limited to quality control factors that determine whether the constituents and dosage forms of drugs are accepted or rejected during or after manufacture. The essential factors in this respect are product quality specifications and production control.

Product quality specifications

Product quality specifications are necessary as standards by which to judge (a) the suitability, for use in manufacture, of starting materials and "half-finished" products, and (b) the quality of end products.

Starting materials. Specifications for starting materials may be found in official compendia, such as pharmacopoeias, codices, and formularies. If official specifications are not available for a given substance, the user will have to draw up specifications for his own use, or agree to those proposed by the manufacturer of that substance.

Specifications for starting materials must be based on the characteristics of processes used to produce them, and should include descriptions of (a) physical characteristics, (b) specific identification tests, (c) purity tests,

and (d) the assay method. Additional specifications may also be included to facilitate the use of a given substance in manufacture.

“Half-finished” products. Specifications for “half-finished” products are of interest principally to the manufacturer. They may be necessary to determine (a) the suitability of such products for further manufacturing operations, or (b) the acceptability of the products, if they are procured from outside sources, for the purchaser’s use in the manufacture of drugs.

Finished (end) products. Specifications for finished products provide, in precise and detailed terms, criteria on the basis of which the designated control authority determines the acceptability of finished drugs.

Production control

Since quality must be “built into” products from the beginning of manufacture, production control is the principal method of maintaining desired quality levels in “half-finished” and end products.

Starting materials and “half-finished” products should be used in manufacturing only after their quality has been found acceptable by testing, the results of such testing being described according to a detailed schedule. In particular, although the necessity for the sterility testing of end products must be acknowledged, the limitations of such testing should be recognized; the adequacy and effects of sterilization procedures and other operations intended to prevent microbial contamination should, whenever possible, be validated to the satisfaction of the responsible authority for each product and operation.

The principal aspects of production control are as follows:

- (1) environmental control, covering the suitability of premises, equipment, and staff;
 - (2) manufacturing control, covering (a) factors inherent in the manufacturing processes that might adversely affect the latter, and (b) adverse extraneous factors, such as contamination of starting materials, “half-finished” products, and end products; and
 - (3) final control of the end products, to ensure that they comply with the established specifications and have been manufactured by the prescribed procedures.
-

Annex 2**GOOD PRACTICES IN THE MANUFACTURE AND
QUALITY CONTROL OF DRUGS****1. General considerations**

In the pharmaceutical industry, overall control is essential to ensure that the individual 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.¹ They are intended to apply to the manufacturing practices (including packaging and labelling) used in the production of drugs in their finished dosage forms.

It not infrequently occurs that several firms co-operate in the production (including packing 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 requirements proposed below. However, packing and labelling do not necessarily affect the quality of a drug, and in such cases it may suffice to ensure that adequate measures are taken as specified in applicable sections of this document.

¹ Additional recommendations specifically applicable to biological products are set forth in a number of sets of Requirements for Biological Substances adopted by the WHO Expert Committee on Biological Standardization and other WHO expert groups and published in the WHO *Technical Report Series*.

The requirements set forth herein are not intended to apply to preparations for veterinary use, although equal attention should be given to quality in the manufacture of such preparations.

2. 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 in (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 man or 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 solely for 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 printed on the label of the drug, 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 kept in isolation and that is not available for use until released.

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

"Half-finished" product. Any material or mixture of materials that must undergo further manufacture.

Purity. The degree to which other chemical or biological entities are present in any substance.

3. Personnel

Experts responsible for supervising the manufacture and 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, physical chemistry, etc.); (b) chemical engineering; (c) microbiology; (d) pharmaceutical sciences and technology; (e) pharmacology and toxicology; (f) physiology and histology; and

(g) other related sciences. They should also have adequate practical experience in the manufacture and 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 independent professional judgement, based on the application of scientific principles and understanding to the practical problems encountered in the manufacture and control of drugs.

Such experts should preferably not have any interests outside the manufacturer's organization that (a) prevent or restrict their devoting the necessary time to their assigned 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 control operations in accordance with established procedures and specifications.

4. Premises

4.1 General

Drugs should be manufactured, processed, packaged, labelled, and tested in isolated areas, which should

- (1) not be utilized for any other purpose ;
- (2) be well lighted and ventilated and, if necessary, heated and air conditioned so as to ensure the maintenance of a satisfactory temperature and relative humidity that will not adversely affect the drug during manufacture and storage, nor the accuracy and functioning of laboratory instruments ;
- (3) be suitable for their intended use (walls, ceilings, etc. should have smooth surfaces and be of such construction that they (a) do not crack or shed particles into the atmosphere, and (b) can be readily cleaned and, if necessary, disinfected) ; and
- (4) provide adequate working space and adequate room for the orderly placement of equipment and materials, so as to (a) minimize or eliminate any risk of confusion between different drugs and their components, and (b) control the possibility of cross-contamination by another drug that is manufactured, processed, packaged, labelled, or held on the same premises.

Special rooms or areas should be provided for the storage of highly toxic drugs and narcotics, and the access of personnel to such rooms or areas should be restricted.

4.2 *Special*

For special purposes, such as the manufacture of drugs that can be sterilized in their final 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 entered through an air-lock. The access of personnel to such areas should be restricted. The areas should, if feasible, be designed so as to 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 noncommunicating areas.

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

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

5. **Equipment**

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

- (1) be suitable for its intended use ;
- (2) facilitate thorough cleaning wherever necessary ;
- (3) exclude 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 apparatus used to sterilize products should be monitored by means of recording devices and/or indicators, which should be initially calibrated and checked at approved intervals by approved methods.

Manufacturing equipment and utensils should be thoroughly cleaned and, if necessary, sterilized, and maintained in accordance with specific written directions. When indicated, all equipment should be disassembled and thoroughly cleaned, to preclude 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.¹ Adequate records of such tests should be maintained.

6. 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.

7. 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 their origin, date of receipt, date of analysis, date of release by the quality control department, and their subsequent use in manufacture. All such materials must be

- (1) identified, and their containers examined for damage ;
- (2) properly stored ;
- (3) properly sampled by the quality control department ;
- (4) tested for compliance with requirements (all materials should be marked to indicate that they are undergoing testing, and should, if possible, be " quarantined " until released by the quality control department) ; and
- (5) released by the quality control department by means of written instructions.

¹ This may be accomplished by conducting normal filling operations using suitable sterile liquid bacteriological media or other media suitable for dry powder filling, as the case may be, or by using biological indicators that can demonstrate the adequacy of the sterilization process.

Starting materials that are accepted or approved should be properly and conspicuously labelled as such, and should then be transferred, if necessary, 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.

8. Manufacturing operations

Manufacturing operations and controls should be carried out under the supervision of experts, as specified in section 3.

8.1 *Cleanliness*

Before any manufacturing operation is begun, a check should be made to ensure that all apparatus and equipment to be used in the operation has been cleaned and/or sterilized (see section 5).

8.2 *Equipment and containers*

The contents of all vessels and containers used in manufacture and storage between manufacturing stages must be identified by conspicuously placed and clearly legible labels, bearing the name and/or identification code of the processed materials and the necessary batch identification data. Such labels should, whenever practicable, be securely attached to the vessels and containers concerned. Similar labels should be attached to mechanical manufacturing equipment during its operation, listing the name and/or identification code of the manufactured product and, where necessary, its batch identification.

8.3 *Precautions against contamination*

All manufacturing operations should be confined to separate areas intended for such purposes, with complete equipment used exclusively in those areas, or measures should be taken to ensure that neither contamination nor confusion can occur.¹

Sterile operations must be performed in areas specially designed and constructed for their intended purpose, as indicated in section 4.2. Whenever the different operations are not physically separated, and there is a possibility that unsterilized and sterilized products might be confused, all containers of batches of products for sterilization should bear a clear indication of whether or not their contents have been sterilized.

¹ It is usually advisable to avoid, whenever possible, the simultaneous manufacture of drugs that are similar in appearance in adjacent areas that are not physically separated.

All operations in which highly potent drugs, including antibiotics, are weighed, mixed, micronized, encapsulated, formed into tablets, placed in containers, etc. should be conducted in confined areas that are provided with adequate exhaust systems or that are maintained under appropriate pressure, so as to prevent one drug from spreading to and contaminating another. Adequate precautions should be taken to prevent the recirculation of contaminated air.

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

Products that undergo sterile operations should be protected from contamination by either (a) using methods such as laminar-flow techniques, or (b) ensuring that personnel wear clean, sterile gowns, head coverings, masks, rubber gloves, and shoe coverings. Before dressing and entering sterile areas, personnel must wash their hands with a suitable disinfectant.

8.4 *Manufacturing personnel*

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. Manufacturing personnel should undergo periodic health checks. In order to prevent any impairment of health caused by the handling of hazardous or potent products, 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 restrict personnel to their immediate working areas.

8.5 *Manufacturing procedures and written instructions*

Manufacturing procedures and written instructions for each drug must be prepared under the direct supervision of experts (see section 3) who have the necessary authority. They should contain at least the following information for each drug :

- (1) name and presentation ;
- (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 material 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.

8.6 *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 analysed in accordance with the manufacturing procedures and written instructions described in section 8.5. A separate batch manufacturing record should be prepared for each batch of drug produced, and should include the following information:

- (1) name and presentation;
- (2) date of manufacture;
- (3) batch identification;
- (4) complete formulation of the batch (see section 8.5, point 3);
- (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 as compared with the theoretical yield (see section 8.5, point 4);
- (7) a duly signed record of each step followed, precautions taken, and special observations 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 applicable, closures used;
- (11) signature of the expert responsible for the manufacturing operations, and the date of his signature; and
- (12) a full analytical report showing whether the batch complies with the prescribed specifications for the drug (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 batch manufacturing records*

For reference purposes, all batch manufacturing records should be retained for a specified period.

9. Labelling and packaging

Labelling and packaging materials, including leaflets, should be stored in such a way as to ensure that the correct labels, etc., are affixed to or accompany any given drug. Access to such materials should be restricted to authorized personnel.

Prior to packaging and labelling of a given batch of a drug, the manufacturing and control records specified in section 8.6 should show that the batch has been duly tested, approved, and released by the responsible quality control expert. Prior to being issued, all labels for containers, cartons, and boxes and all circulars, inserts, leaflets, etc. should be examined and released as satisfactory for use by the designated authority.

To prevent packaging and labelling errors, a known number of labels should be issued and properly coded. Such issuance should be made against a written, signed request that indicates the quantity and type of labels required. Upon completion of packaging and labelling, the number of labels actually used should be carefully compared with the number issued and coded. Destroyed and unused labels should also be checked.

All finished drugs should be identified by labels 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 ;
- (3) the batch number assigned by the manufacturer ;
- (4) the date of manufacture and/or the expiry date, as required (if desired, the date of manufacture may be given as a code) ;
- (5) the name and address of the manufacturer ;
- (6) any special storage or handling precautions that may be necessary ;
- (7) indications and directions for use and any warnings and precautions that may be necessary.

10. The quality control system

Every establishment that manufactures pharmaceuticals should have a quality control department that is autonomous in the areas of responsibility assigned to it. It should control all starting materials, monitor the quality aspects of manufacturing operations, and control the quality and stability of drugs.

A quality control laboratory must also be available. The laboratory should :

- (1) be adequately staffed and fully equipped for performing all quality control tests and analyses required during and after manufacture;¹
- (2) be supervised by a qualified expert (see section 3), who should have the final responsibility for approving or rejecting all materials tested;
- (3) be promptly informed of all changes and modifications in the manufacturing procedures and written instructions (see section 8.5).

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 control and release each batch of starting material;
- (3) to control and release "half-finished" products, if necessary;
- (4) to control and release each batch of finished drug that is ready for distribution;
- (5) to control and release packaging and labelling materials and the final containers in which drugs are to be placed;
- (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 expiry dates and shelf-life specifications, whenever necessary, on the basis of stability data; and
- (9) to establish (and, when necessary, revise) control procedures and specifications.

In order to fulfil its responsibilities, the quality control department should take samples in sufficient quantities, according to established procedures, and keep appropriate analytical records. The samples should be properly labelled, and portions should be kept for future reference.

The quality control department should maintain adequate analytical records concerning the control of each batch of drugs manufactured. Such records should include:

- (1) a final evaluation of the product and a decision as to whether or not the analysed and controlled batch conforms to the established specifications;

¹ If animal tests are necessary, the animals should be given adequate quarters and care (for further information, see *Wld Hlth Org. techn. Rep. Ser.*, 1966, No. 323, pp. 14, 16). The use of outside independent laboratories may be advisable for specialized and complex analytical and biological procedures that require the use of costly equipment and that can be performed only by technicians with specialized training. Such laboratories should be adequately staffed and fully equipped to perform such analyses.

- (2) the source of the specifications used ;
- (3) the signature(s) of the person(s) who performed the quality control procedures ; and
- (4) a final review and dated endorsement by a duly authorized expert.

The quality control department should also be responsible for the full 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.

11. Self-inspection

In order to maintain strict adherence to all manufacturing procedures and prescribed controls, it may be advisable for a firm to designate an expert or a team of experts to conduct regularly scheduled inspections of its overall manufacturing and control operations. However, this should not be taken to mean that any firm electing to exercise self-inspection should be exempt from the official inspections required by the laws and regulations of the country in which it is located.

12. Distribution records

Adequate records should be maintained of the distribution of a finished batch of a drug in order to facilitate prompt and complete recall of the batch if necessary.

13. Complaints and reports of adverse reactions

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

Annex 3

ANALYTICAL DATA ON DRUGS

The questionnaire referred to in section 5.2 of this report would request the following information from manufacturers of drugs.¹

(1) Name and address of organization supplying the information, and of the individual to whom queries should be addressed.

(2) Details and dates of approval of the drug by national control authorities.

(3) Name of the drug (international non-proprietary name, where available); trade name; chemical name; molecular formula and molecular weight; graphic formula.

(4) Description, including physical form, colour, odour, taste, appearance of solution, and whether the drug is hygroscopic.

(5) Solubility in grams per 100 ml of water, ethanol, ether, chloroform, and other solvents, at a stated temperature.

(6) Physical data, including (a) melting range; ² (b) freezing point and congealing point; (c) boiling range; ² (d) refractive index; ² (e) optical rotation (sodium light, mercury light); ² (f) density in g/ml at a stated temperature; (g) spectral absorption (ultraviolet, infrared, nuclear magnetic resonance); ³ (h) viscosity; ² and (i) pKa.

(7) pH of a solution of stated concentration, and titratable acidity or alkalinity.

(8) Chemical reactions suitable for identification (if possible, the degree of specificity should be stated) and physical characteristics suitable for the same purpose.

(9) Water content: (a) loss of weight on drying, under stated conditions; (b) Karl Fischer titration; (c) azeotropic distillation followed by

¹ Not all the information requested is applicable to every drug. If any section of the questionnaire is not completed, the reason should be indicated — i.e., whether the information is not available or inapplicable. Information that the manufacturer desires to be kept confidential should be indicated.

² Where applicable, full details should be given of the method, apparatus, and reagents used.

³ Full details should be given of the apparatus and methods used, and curves should be supplied.

Karl Fischer titration ; (d) near-infrared spectroscopy ; and (e) gas chromatography.

(10) Residue on ignition by a stated method.

(11) Description of assay method, including data on its accuracy and precision, and information on whether the method reflects the therapeutic activity of the substance and whether it can be used for all available dosage forms.

(12) Results of purity tests, including (a) tests for heavy metals and information on emission spectra, if these have been obtained ; (b) tests for residual impurities or decomposition products ; (c) thin-layer chromatography (including information obtained with as many different solvent systems and spray reagents as possible, and information on whether artefacts are likely to form during chromatographic procedures) ; (d) phase solubility tests ; and (e) thermal analysis. If impurities have been identified, details should be given.

(13) Any other information that may be necessary for characterization of the drug and for its safe and effective use in pharmaceutical preparations (e.g., biological tests such as toxicity tests).

(14) Conditions recommended for storage of the drug, and information on factors that are likely to affect its therapeutic activity during storage and shipping.

(15) Brief description of the principal pharmacological category to which the drug belongs, and information on its proposed therapeutic uses. (Such information is in no way intended to be binding on prescribers.)

(16) A provisional monograph that clearly states the tests and limits to be used in determining the acceptability of the drug.

Manufacturers would also be requested to provide adequate samples of drugs.

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