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TWENTY-FIRST WORLD HEALTH ASSEMBLY

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QUALITY CONTROL OF DRUGS

Report by the Director-General

1. In resolution WHA20.34,[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, the Assembly requested the Director-General to report, through the Executive Board, to the Twenty-first World Health Assembly, "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."

2. The Executive Board studied the Director-General's report on the matter and in resolution EB41.R28[2] requested the Director-General "to submit the report to the Twenty-first World Health Assembly together with any supplementary information he may deem useful and the summary records of the discussions during the forty-first session of the Board."

The report of the Director-General to the Board is annexed to this document, as Appendix 1. The summary records of the discussions at the forty-first session of the Board are also attached, as Appendix 2. It has been felt advisable to reproduce the report in its original form as the discussions in the Board relate closely to it; supplementary information which is deemed useful is given hereafter.

3. As requested in the first operative paragraph of resolution EB41.R28, the formulation of generally acceptable requirements for good manufacturing practice for the production and quality control of pharmaceutical products has been pursued and the draft requirements, as reproduced in the annex to Appendix 1, have since been sent to governments of Member States to enable their technical services to study them in detail and to prepare any comments governments would wish to make, either in the course of the discussions in the Assembly or in writing; this step was considered essential to ensure the widest possible acceptability of such requirements, which will provide an indispensable basis for the satisfactory performance of quality control.

Comments received will be duly taken into account in the drawing up of the final text with the assistance of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, later in the year.

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[1] Handbook of Resolutions and Decisions, 9th ed., pp. 114 and 115.

[2] Off. Rec. Wld Hlth Org., 165, p. 16.

4. The question of "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", as per operative paragraph (iv) of resolution WHA20.34, is dealt with in the two attached appendices and will not be further commented upon here.

5. Continued attention has been given, during the year, to the need for the Organization "to assist Member States in establishing or securing access to national or regional laboratory facilities for the quality control of drugs", as prescribed in operative paragraph (iii) of the above-mentioned resolution.

Growing interest in this aspect of the problem on the part of governments, particularly of developing countries, is evidenced by the many requests for assistance directed to the Organization, in all the Regions, either for country projects geared to the establishment of the necessary facilities for quality control or for inter-country activities - such as seminars or consultant services - directly related to the subject. These requests are reflected in the Proposed Programme and Budget Estimates for 1969.[1]

As reported earlier, the need for international support in this field has been recognized, too, by other institutions, from the technical assistance, pre-investment and investment points of view. Interest for such support has already been indicated by the United Nations Development Programme (UNDP); preparatory studies are being made for the setting up of a national control institution in India and of a national institute in Uruguay for the training of personnel in South America, both of which would hopefully qualify for UNDP's assistance. The Inter-American Development Bank has expressed interest in the latter.

Furthermore, there are definite indications that a good deal of external help may be provided under bilateral schemes. The Director-General is endeavouring to collect information on such schemes, in order to gain as comprehensive a picture as possible of the existing situation and to ensure adequate co-ordination of efforts.

A considerable task lies ahead for Member States and for the assisting multilateral and bilateral agencies in this domain; complex technical and organizational issues are involved, as well as the necessity to train, in sufficient numbers, the personnel required.

Special emphasis is being laid on training activities, as a preliminary step essential to institutional development; these include individual fellowships and training courses and seminars.

A training course for the quality control of drugs was held in Copenhagen, in March 1968, in collaboration with the Danish Board of Technical Co-operation with Developing countries and the National Health Service of Denmark. This course, which was the first of its kind, lasted three weeks and dealt with different aspects of quality control, through both theoretical and practical training. Similar courses are contemplated for the future. Seminars on the subject are being planned in the South-East Asia and Western Pacific Regions, for 1968 and 1969 respectively. The training institute to be set up in Uruguay, as mentioned above, will, it is felt, go a long way towards meeting the needs of countries in South America in the same respect.

Concurrent efforts will be made to promote co-operation among countries with a view to their gaining access to existing national facilities for the purpose of quality control of drugs. An excellent illustration of this type of co-operation is given by the national quality control laboratory in Panama, which the Council of Health for Central America and Panama has decided to use for the six countries of which it is composed.

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[1] Off. Rec. Wld Hlth Org., 163.

6. Attention has been repeatedly called, lastly by the Twentieth World Health Assembly in operative paragraph (v) of resolution WHA20.34, on the need for "countries which export pharmaceuticals to ensure that these are subject to control measures which will secure that they comply with standards of quality not less than those imposed on domestic commerce".

As requested by the Assembly, the Director-General has brought this resolution, and particularly its paragraph (v), to the attention of all governments.[1]

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

EXECUTIVE BOARD

EB41/38
11 January 1968

Forty-first Session

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Provisional agenda item 2.6.1

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

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[1] 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 Expert Groups and published in the Technical Report Series.

[2] NOTE: Various other definitions, previously proposed elsewhere, were also considered, but for the purpose of this text the present definition was agreed upon.

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.

WORLD HEALTH ORGANIZATION

ORGANISATION MONDIALE DE LA SANTÉ

EXECUTIVE BOARD

Forty-first Session

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SUMMARY RECORD OF THE TENTH MEETING

WHO Headquarters, Geneva
Monday, 29 January 1968, at 9.30 a.m.

CHAIRMAN: Dr K. N. RAO

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Tenth Meeting

Monday, 29 January 1968, at 9.30 a.m.

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Dr D. BADAROU, Rapporteur	Dahomey
Dr M. P. OTOLORIN, Rapporteur	Nigeria
Professor E. AUJALEU	France
Dr J. C. AZURIN	Philippines
Dr A. BENYAKHLEF	Morocco
Dr E. A. DUALEH	Somalia
Dr A. ENGEL	Sweden
Dr C. K. HASAN	Pakistan
Dr A. A. AL-HURAIBI	Yemen
Dr H. M. EL-KADI	United Arab Republic
Dr O. KEITA	Guinea
Dr I. KONE (alternate to Dr B. N'Dia Koffi)	Ivory Coast
Professor L. von MANGER-KOENIG	Federal Republic of Germany
Professor I. MORARU	Romania
Dr R. A. MORENO	Panama
Dr G. A. NOVGORODCEV (alternate to Dr D. D. Venediktov)	Union of Soviet Socialist Republics
Dr V. V. OLGUÍN	Argentina
Dr PE KYIN	Burma
Sir William REFSHAUGE	Australia
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Secretary: Dr M. G. CANDAU
Director-General

Representatives of Intergovernmental Organizations

United Nations	Mrs W. J. E. de BOIS
United Nations Relief and Works Agency for Palestine Refugees in the Near East	Dr M. SHARIF
Organization of American States	Mr H. L. HERNÁNDEZ

Representatives of Non-governmental Organizations

Council for International Organizations of Medical Sciences	Dr V. FATTORUSSO
International League of Dermatological Societies	Professor J. GAY-PRIETO
International Pharmaceutical Federation	Dr E. LANG
International Union of Pure and Applied Chemistry	Dr R. MORF
League of Red Cross Societies	Professor A. LIBOV
Medical Women's International Association	Dr Anne AUDÉOUD-NAVILLE
World Federation for Mental Health	Dr Anne AUDÉOUD-NAVILLE

1. PHARMACEUTICAL PREPARATIONS: QUALITY CONTROL OF DRUGS: Item 2.6.1 of the Agenda (Resolution WHA20.34; Document EB41/38)

The CHAIRMAN invited Dr Bernard to introduce the item.

Dr BERNARD, Assistant Director-General, said the report before the Board (document EB41/38) was being submitted in pursuance of resolution WHA20.34.

Three suggestions were made in the report as to the principles that might be embodied in regulations under Article 21 of the Constitution or recommendations under Article 23: (1) certification by WHO that drugs destined for exportation complied with established international standards of quality; (2) certification by the government of the exporting country that any drug destined for exportation complied with standards of quality not less than those imposed for consumption in the country of origin; and (3) certification by the government of the exporting country that any drug destined for exportation had been produced in compliance with good manufacturing practices. The Director-General had gone carefully into all three suggestions (document EB41/38, paragraphs 3-5) and had reached the conclusion set out in paragraph 6 of the report, namely, that possible regulations to be established under Article 21 of the Constitution might provide for a certificate to be issued by the manufacturer, which certificate would be endorsed by the national authority of the exporting country. The manufacturer's certificate would contain a full description of the quality specifications of the drug and of the test methods applied, together with additional data on packing materials, transport and storage conditions, expiry date where applicable, and conformity of labelling to requirements. Endorsement by the national control authority would be subject to the manufacturer meeting the requirements of good manufacturing practices to be recommended under Article 23 of the Constitution, as attested by regular plant inspection by the authority in question; and to the drug or pharmaceutical specialty complying with the established quality specifications, as witnessed by random sampling and testing.

Obviously, certification of the kind should be based on universally recognized standards in manufacturing practices. The work already begun in that area had been continued since the last Health Assembly, with the assistance of experts and a small advisory group. As a result, draft requirements for good manufacturing practices were annexed to the Director-General's report.

Certificates of the kind mentioned would not entirely dispense with the need for quality control of drugs by the importing country, which should possess or have access to control laboratories for random checking of imported products designed to detect possible deterioration during transport and storage. The development of national or regional laboratory facilities for that purpose would be determined by the availability of financial and human resources, together with the necessary administrative and legal basis. Work toward the setting up of control institutions was already well advanced in a number of places (document EB41/38, paragraph 9). The Secretariat had been trying to collect more information on the various countries and the Director-General hoped to be in a position to expand the information in reporting to the Health Assembly.

Internationally recognized specifications for pharmaceutical quality control and the existence of reference substances for analytical work were a prerequisite for satisfactory control; such specifications were now available in the second edition of the International Pharmacopoeia.

Professor MACÚCH commended the Director-General on the report, which made an excellent analysis of the problem in quality control of drugs. Once the proposals contained in the report were adopted and ratified by Member States there would be assurance of good control of drugs entering into international commerce, provided there was good co-operation between the countries of import and of export. In that regard, the requirements for good manufacturing practice laid down in the annex were of paramount importance. There was undoubted need for permanent quality control of drugs from the point of production to the point of consumption, and that control should extend to new drugs entering into international

commerce. Accordingly those requirements should be given consideration and should be adopted as the basic element in any additional measures to be taken. He therefore supported their issue as a WHO recommendation under Article 23 of the Constitution.

The work of countries now engaged in establishing their own specifications for pharmaceutical quality control would be greatly facilitated by the work that had gone into the second edition of the International Pharmacopoeia.

Dr ENGEL joined in congratulating the Director-General on the report before the Board, underlying which lay a great deal of effort. He particularly welcomed the requirements for good manufacturing practice set out in the annex, as the core of international regulations to secure quality control of drugs; the requirements would be of the utmost importance for maintaining a high standard in pharmaceutical preparations throughout the world.

The discussions on the subject over the years had plainly brought out the importance of means to control drugs destined for exportation. However, his own interest was especially focused on manufacturing procedures. The requirements as laid down were very technical and would need pharmaceutical experts to assess their value. All Member States had been awaiting the guidelines they represented and all drug manufacturers of good reputation were anxious to meet the highest requirements. The difficulties lay, however, in controlling the very small manufacturing firms. If the requirements were issued as a WHO recommendation they would be of great use to countries in eliminating the worst offenders among such small firms.

Well drawn up regulations would be effective only if the countries established a national control agency under the national health administration to cover, in addition to pharmaceutical control, environmental control from the public health standpoint. Accordingly, it was extremely important, as laid down in part B of the draft requirements, that Member States should adopt legislative measures to enforce the control system and give the national health administrations the means needed for effective inspection. Much was said about chemical cleanliness and contaminants; both terms should be taken to refer to chemical and microbiological contaminants.

In conclusion, he again commended the report as of great value in advancing the aim of good quality control of drugs; he hoped that further action on its recommendations would be successful.

Professor MORARU advocated that the following general principles should be taken into account for guaranteeing the quality control of drugs entering into international commerce: the preparation should be accompanied by a detailed certificate of control, to be issued by the national control agency; quality standards should be established on the joint basis of the International Pharmacopoeia and the national pharmacopoeias of the two parties concerned (where specifications did not appear in any of the three pharmacopoeias, they should be drawn up jointly by the parties concerned and the labelling should show the technical specifications and the methods applied in their control). International comparability of methods applied in quality control of drugs was needed; where they did not exist, control should be exercised in accordance with the methods laid down in the International Pharmacopoeia. Additions to those methods should be published periodically by WHO.

Professor von MANGER-KOENIG said he had studied the report carefully and as far as he could judge it provided positive answers to the questions propounded by resolution WHA20.34. The Director-General's proposal in respect of international regulations for the quality control of drugs appeared to be realistic enough to merit the Board's close attention. The principles outlined in paragraph 6 of the report, although perhaps not in final form, seemed to be relatively well formulated and clear enough for submission to the Health Assembly. The concept of separating the procedure into two parts made it all the more likely to be practicable. The regulatory part would deal with the modalities of certification, which modalities would not be open to frequent modification. On the other hand, the recommended manufacturing practices would probably require to be brought up to date periodically. In short, the report outlined a balanced programme and much would be achieved if resources enabled it to be put into effect. The international work and

arrangements would, of course, have to be supplemented by national legislation and national control through a national control agency. The work at the national level would require an increase in training arrangements.

Dr BENYAKHLEF joined in congratulating the Director-General and the staff on the excellent report before the Board. The question of quality control of drugs was of great importance both for manufacturing and importing countries, and more particularly for the latter where they depended wholly upon imports for their supplies. Manufacturers in many countries, when entering bids, were in the habit of giving guarantees on quality; however, so many of the drugs entering into international commerce had no trade names and importing countries found it difficult to recognize some among them. Also, with the need for most of them to husband resources in foreign exchange, they were inclined to settle for the cheaper variety which might be of bad quality. Under Article 21 of the Constitution, the Health Assembly was empowered to adopt regulations bearing on the safety of pharmaceutical products and drugs. In the circumstances, therefore, it should be asked to take more stringent action against drugs not up to standard.

Dr NOVGORODCEV said the matter was of mutual interest to the developed and developing countries and the latter had repeatedly asked WHO to take effective control measures. The measures now under consideration were therefore worthy of support. Indeed, all the work done by WHO in standardization of drug specifications should be regarded as of great value. The Organization was to be commended, for example, on the recently issued recommendations on temperature control of drugs which had aroused great interest in the European Regional Committee.

The proposed requirements for good manufacturing practice certainly deserved attention, but as had already been pointed out, specialists would be needed to assess their applicability. On the whole they seemed to be good recommendations based on expert advice, and thus could be given general support. The fact that manufacturing countries would be obliged to provide quality control services was of paramount importance, since it would to some extent protect the importing countries against inadequate standards.

On the matter of certification, he pointed out that in his own country the same quality standards were applied in respect to drugs irrespective of whether they were destined for internal or external consumption. The measures proposed might therefore in the first instance take on the form of a recommendation rather than an international regulation, to see what effect that action might have.

Lastly, the measures laid down in regard to the International Pharmacopoeia should not supersede the work on drug specifications being done by the countries themselves.

Professor AUJALEU remarked that the Health Assembly had placed the Secretariat in a difficult position by passing on to it the hard problem of the quality control of drugs; in the circumstances, the Secretariat had done its best. For his own part, he was very concerned at the way the Organization was proceeding in the matter. It was gratifying, of course, that international control by WHO of drugs entering into international commerce had been set aside, for materially and financially, such control would be impossible to effect. On the other hand, the proposals made seemed to him to go too far. Regulations under Article 21 of the Constitution would have to be accepted by most countries in order to remain in good international standing but in actual fact, and on a scale much more difficult to detect, the same would happen as happened in respect to the International Sanitary Regulations. There, every country had undertaken to ensure that the measures laid down would not be exceeded but the moment a serious epidemic threatened excessive measures were put into force. And all the Organization could do was to take note of such departures from the allowable. In the present instance, regulations left to the control of the national authority, i.e. the drug-producing country, would simply embarrass honest countries and give those less so all the latitude they wanted.

In his opinion, the concept of equal quality in drugs, whether for export or for utilization in the producing country, would offer guarantee enough and also fewer disadvantages. Undoubtedly, if a drug was considered of adequate quality for consumption in the

producing country, it might surely be accepted as valid for use in other countries. A simple procedure might be evolved to cover the few cases of drugs not utilized in the producing country because of the absence of the diseases against which they were directed. He would accordingly prefer resort to recommendations under Article 23 of the Constitution rather than regulations under Article 21, since in the one case the Organization's authority would be less committed than in the other. The attention of the Health Assembly should be drawn to those matters.

He would add that the best solution seemed to lie in further help by WHO to national and regional control laboratories. In that regard, it must be borne in mind that countries that were technically weak today would be less so tomorrow, and the kind of trusteeship represented by regulations was not really advisable. In short, he favoured recommendations under Article 23 of the Constitution and expanded assistance from WHO to national or regional control laboratories in order that the countries themselves might effect control with the help thus made available.

Dr WATT joined in thanking the Director-General for the informative report, which helped to focus attention on an aspect somewhat left aside in the earlier discussions on the subject. Too much had been said there about the problem as affecting the importing and the exporting countries, without making plain that control was needed from the point of manufacture to the point of consumption. Between those two extremes, a varying degree of control - or no control - was exercised, and in addition there had been considerable confusion about whether a drug, a pharmaceutical preparation or an in-between mixture was in question. By focusing attention on good manufacturing practice, one end of the scale was being tackled, i.e. the point of origin. Possibly it might be difficult to enforce recommended practices, but if any manufacturer failed to comply with the requirements as laid down his products would be open to suspicion. And consistent failure as judged by the end product would lose him trade or even lay him open to suit for redress at law, which would be a better protection for the importing country.

He, too, was somewhat concerned about the nature of the Board's recommendation on the matter to the Health Assembly. He was not sure that investigations had gone far enough or deep enough to ascertain where the real problems might lie. The matter of good manufacturing practice was a complex one, and nothing was as yet known as to possible reaction by manufacturers to the proposed requirements. Presumably, the Secretariat had that matter in mind, but whether or not it could ascertain reactions between now and the Health Assembly was open to question. For that reason he was somewhat hesitant about how far the Board could go in recommending the requirements for adoption.

Lastly, the Board in deciding upon its recommendations must also bear in mind possible help by WHO in the matter of national control machinery (document EB41/38, paragraph 9). On the other hand he failed to see how WHO could certify that drugs destined for export complied with established international requirements. Action on those lines would be beginning at the wrong end for, so far as he understood the problem, the difficulties were more likely to arise nearer to the point of consumption. Even if such a procedure was practicable and feasible, he was not sure that the end result would be to give the importing countries the kind of help they needed. It might be helpful to the discussion if more information could be given on the matter of the financial implications of the proposals.

Dr OTOLORIN added his congratulations to the Secretariat on the report under consideration. As always, the Director-General had made a sincere and honest effort to tackle what was admittedly a difficult problem.

The two aspects of the question had been plainly brought out in the discussions at the World Health Assembly. First, there was the moral aspect. It was still true today that some drug exporting countries maintained that the standards of quality control required for drugs for internal consumption need not be adhered to in respect of drugs destined for export. Applied to medicine that attitude was immoral, the more so as many importing countries had no means at their disposal for testing the quality of imported drugs. Past experience showed the need for clearing up that anomaly. By law every country should ensure that drugs, irrespective

of destination, should all conform to the same standards. All that was necessary to protect the importing countries in the matter was for the Director-General to obtain information showing which countries complied with that moral requirement and which refused to comply with it. In that way, the importing countries would have some guidance at their disposal. He would reiterate that what was required was for the manufacturing country itself to lay down the necessary requirements under its own legislation.

The second aspect related to the question of getting drugs of good quality to the patient. The problem there was a more difficult one and the report clearly outlined its complexity. It was manifestly impracticable for the exporting country to take steps to test every drug consignment for export, but that was hardly necessary, for reliance in control was largely based on sample testing. It should be possible for WHO to be able to say that a particular country met the conditions laid down for good manufacturing practice, possibly through a special team that might be invited by the country to examine practices, after which a certificate acceptable to all importing countries might be issued. But much could happen between dispatch and consumption. It would therefore still be necessary for the importing country to have either its own quality control laboratory or access to such a laboratory. Reference was made in the report to efforts to establish control laboratories on a regional basis for South-East Asia and Latin America; but no mention was made of such work in connexion with other regions and in Africa no control laboratory existed outside South Africa. He would therefore like to ask whether the Director-General was in a position to be able to offer the African countries and others in the same position immediate access to quality control laboratories. Past efforts, although highly appreciated, still left much to be done, especially in that matter of getting access to quality control laboratories in order that all countries might be able to check that drugs coming in met the claims of good quality.

Dr AZURIN said that the ideal solution would of course be that mentioned in paragraph 2 (i) of document EB41/38, namely, certification by WHO that the drugs destined for export complied with established international standards of quality. He realized, however, that such action would be beyond the present possibilities of the Organization, though he wondered whether it might not be undertaken partly by exporting countries and partly by WHO.

The most practical of the suggestions was the one in paragraph 2 (iii), namely, certification by the government of the exporting country that any drug destined for exportation had been produced in compliance with good manufacturing practices. No indication was given, however, of how it might work out in practice, and he would like to hear from the Secretariat how it was proposed to make it operative.

Sir William REFSHAUGE congratulated the Director-General on the report. The problem was very complex, and whatever method of control was adopted, the result could not be guaranteed. He agreed with Professor Aujaleu that if it could be guaranteed that drugs for export were of the same standard as those used in the exporting country it would go a long way towards ensuring good quality. He also agreed with Dr Watt's remarks concerning good manufacturing practice.

The requirements in the annex to document EB41/38 appeared sound in a general way, but he would hesitate to say whether they could be put into practice. He was somewhat concerned about how the matter was to be submitted to the Health Assembly. In his view, all the Board could do was to note the report and transmit it to the Health Assembly, at which governments with manufacturing industries of good repute could put forward their ideas.

He was undecided which recommendation was the better - the one in paragraph 2 (ii) or that in paragraph 6, and would like to have more time to consider the matter. Regular inspection was valuable to ensure a high standard of manufacturing practice, but random sampling did not guarantee the quality of the rest of the consignment.

He would like to hear the views of other members as to how the matter should be transmitted to the Health Assembly.

Dr BERNARD thanked members for their comments. After examining the various possibilities, the Director-General had concluded that the most realistic alternative was the one concerning certification by the government of the exporting country that any drug destined for export had been produced in compliance with good manufacturing practice, and he had embarked at once upon a study of what should constitute good manufacturing practice.

In reply to the point raised by Professor von Manger-Koenig, he said that the annex to document EB41/38 represented only a stage, not a finished product. Very simple principles had been presented as a result of the work by the Secretariat with the assistance of some consultants. It was hoped to draw up more elaborate standards with the help of experts and in contact with the International Pharmaceutical Federation - a non-governmental organization in official relations with WHO with which a close working relationship on such problems existed - and to submit them to the Expert Committee on Pharmaceutical Specifications at its meeting in 1968. It was thus hoped to be able to give the Health Assembly the most extensive technical support possible when it came to adopt recommendations or regulations on the subject.

A number of members had emphasized the importance of control in importing countries, as mentioned in paragraph 9 of the report, and Dr Otolorin had mentioned the possibility of WHO's helping importing countries to have access to a qualified control laboratory for the purpose. Professor von Manger-Koenig had also emphasized the need for training of personnel. While concentrating on standards of manufacture, the Director-General had not lost sight of that aspect.

In paragraph 9 of the report reference was made to a centralized quality control institution to serve the needs of several countries in Latin America. Two things, however, had been combined in that statement. There was in Panama a quality control laboratory attached to a university, which functioned in conjunction with the Ministry of Public Health, and the Health Council for Central America and Panama had decided to use it for the six countries of which it was composed. That was an excellent example of a national control laboratory that could be used by a number of neighbouring countries. Secondly, a proposal was at present being presented to the United Nations Development Programme for the setting up of an institute in Uruguay for training control personnel in South America. The Inter-American Development Bank had shown an interest in the project.

With regard to the question of the attitude to be adopted by the Board, and the form of its presentation to the Health Assembly, resolution WHA20.34 requested the Director-General to report to the Twenty-first World Health Assembly, through the Executive Board and with its comments. The Board might perhaps consider recommending the Director-General to present the report to the Health Assembly with any additions or amendments that might appear justified by experience and information acquired during the coming months, and to append to it the summary record of the Board's discussions on the matter. That procedure would perhaps meet the Health Assembly's wishes.

Dr MORENO expressed gratification at the establishment of the laboratory in Panama which, as well as having taken responsibility for the quality control of pharmaceutical preparations, carried out periodic testing of foodstuffs. It had also made proposals for the development of a training programme. Its efforts were worthy of support by WHO.

Dr ENGEL said that the most essential point was good manufacturing practice, which was at present a missing link in the control chain. Most Member States must feel the need for technical and ethical guidance from WHO. He maintained his view that regulations should be applied under Article 21 of the Constitution.

Dr OLGUIN emphasized the importance of national control legislation in both exporting and importing countries. Regional centres were needed for carrying out control activities with national and international support, and staff training was necessary. The question of the Organization's role was complex. Application of Article 21 of the Constitution, however, would deal with the most important problems, since it gave the Health Assembly the authority to adopt regulations on the matter.

Dr WATT pointed out that the coming into force of regulations adopted under Article 21 was subject to the terms of Article 22, which stated:

> Regulations adopted pursuant to Article 21 shall come into force for all Members after due notice has been given of their adoption by the Health Assembly except for such Members as may notify the Director-General of rejection or reservations within the period stated in the notice.

He recalled the discussion that had taken place concerning the problem of possible reservations with regard to the International Sanitary Regulations. In the present case, if the provisions of Article 23 were applied, the complication of possible reservations would not arise, and he thought that article preferable, therefore, at the present stage, to Article 21.

Dr BADAROU said that the question was a most important one, and had been discussed on a number of occasions, as could be seen from resolution WHA20.34. As far as he was concerned, the problem was to achieve some specific results within the shortest possible time, since drugs were still circulating in international traffic without having been subjected to adequate control. Dr Benyakhlef had emphasized the problem confronting certain States with limited resources that were being offered highly publicized drugs at a comparatively low cost, and the consequent tendency to purchase them to the detriment of the health of their populations. He would like the Board to recommend that the Health Assembly use its authority to establish international regulations. Dr Watt had emphasized that some countries might fail to apply them, but in that case they would be risking a loss for their pharmaceutical industries.

He would like countries to be afforded the means of controlling the toxicity, efficacy and purity of drugs, and since the setting up of laboratories was very costly, the Health Assembly should be requested to support the establishment of regional laboratories - a step that would offer an easy solution to the problem that had been under discussion for so long.

Dr OTOLORIN said that, if it were considered more expedient to proceed under Article 23 of the Constitution, in accordance with Dr Watt's suggestion, it could well be done. It would still presumably be necessary, however, for the Director-General to obtain information as to the number of countries that had accepted the recommendations. If it were impossible to get the information, the procedure would not be very valuable to importing countries.

Sir William REFSHAUGE supported Dr Watt's remarks. He realized the importance of the matter, but it was also important to produce results. The ideal would of course be eventually to apply Article 21. Although the matter had been before the Health Assembly on many occasions, however, any recommendations had been in general terms and there had been no specific guidelines for manufacture. He considered that it would be possible to do more by using the terms of Article 23 first and moving on to the provisions of Article 21 more gradually. It would be of no benefit to apply that article if all the major manufacturing countries were to make reservations.

Dr AZURIN also supported Dr Watt's proposal that the terms of Article 23 should be applied.

Dr KEITA said that when the question had been discussed at a previous session, his remarks had been misunderstood as meaning that there should be one control laboratory in each country, whereas what he had spoken of had been the need of one per region. Regional laboratories would be less expensive and would enable countries with no facilities of their own to carry out the necessary control activities.

The report was well presented and responded exactly to the points made in resolution WHA20.34, and he saw no reason for delay in proceeding to a more practical phase in its application. The Board had to make proposals to the Health Assembly for decisions concerning its responsibility. At least two years' work had been devoted to the matter; principles and rules had been drawn up that had been well studied and well presented, and that could form the basic elements for regulating the problem. When regulations were adopted by States Members

of the Organization they were given force of law in the majority of countries. The International Sanitary Regulations, mentioned by Dr Watt, were in fact a case in point. The country from which he came applied them as a law even though the Organization had no political power over that country. He was sure that countries would have no difficulty in applying such regulations, given some flexibility and the possibility of bringing them in gradually, over several years. The regulations envisaged under Article 21 were prerogatives of the Health Assembly. To apply them would not be anti-constitutional and would be a step forward. While the problem was being discussed at such length and at such a slow pace, harmful drugs continued to circulate and populations to be exposed to their dangers, and no measure had been taken against those states or companies producing such harmful drugs. If, however, there were international regulations on the subject, he was certain that producers would think twice before putting harmful or poor quality drugs on the market. The problem should be viewed objectively and not postponed indefinitely while countries with no laboratory facilities and few resources went on buying the cheaper products that might be harmful. He appealed to the Board to support the application of Article 21, regulations under which could of course be revised as necessary, as was being done in the case of the International Sanitary Regulations.

Professor AUJALEU said that he would like to add a few points to his previous intervention. The first was that, in expressing a preference for the application of Article 23, he had had in mind not only the recommendations relating to good manufacturing practice, but also the need to ensure that drugs exported were of the same quality as those for consumption in the exporting country. That point should be added to any recommendations made under Article 23, and should also be included if and when regulations were adopted.

Secondly, the requirements for good manufacturing practice could be compared in some measure to the revision of the International Sanitary Regulations. The Director-General had wisely pointed out in that connexion that the Board was not competent to judge the matter and that it would be preferable for governments to examine it in the intervening period and discuss it in the Health Assembly. He proposed that the same procedure should be followed in regard to the requirements for good manufacturing practice.

Finally, many subjective elements entered into the definition of what constituted a good drug. It was less simple to estimate a good drug than a good health measure. That was an additional reason why he would not like to see the adoption of formal obligations in the form of regulations. In defining the efficacy of a drug opinions could differ somewhat, as was illustrated by the example of cortisone at the time of its discovery and now, fifteen years later. It was necessary therefore to proceed with caution.

Dr MARTÍNEZ agreed with Professor Aujaleu's remarks. In the document to be submitted to the Assembly, a paragraph might be included emphasizing the part to be played by the Organization, which consisted essentially in taking the required measures for co-ordinated development of all the means available to ensure drugs of good quality in all countries. There should be a programme aimed at using all possible means at national and international level to ensure international control at all stages of manufacture.

Dr NOVGORODCEV supported Dr Watt's proposal for the application of Article 23 of the Constitution. Countries should be protected against an influx of poor quality drugs. He agreed with Dr Otolorin that States accepting the recommendations should so inform the Director-General, and that a list should be made available to importing countries to enable them to decide from which countries to import.

Dr KEITA said that while regulations were usually adhered to that was not always the case with regard to recommendations. Developed countries had less cause for alarm, since they were producers, and also had laboratories at their disposal. That was true of the USSR, the United States and France, whereas Dahomey, Guinea, Nigeria and other such countries had no such facilities. The application of Article 21 would be a step in the right direction since international regulations would be more binding upon States and laboratories producing drugs.

Professor AUJALEU pointed out that he had not spoken in the name of France.

Dr KEITA said that neither had he spoken in the name of Guinea. He had mentioned certain States from which members had come, but had not referred to those members as delegates.

Dr BADAROU said that resolution WHA20.34 related to two aspects of the problem; one concerning regulations or recommendations and the other concerning control laboratories. In his view, if a regulation was not binding on all Member States, a recommendation was even less so. In a problem as important as drug control the strongest possible measures should be taken, and since regulations were stronger than recommendations he would prefer them even if they were not entirely effective. One should aim at the ideal even if it appeared Utopian.

The question of the setting up of control laboratories was a very important matter for those that did not have them, and he would like the Board to adopt a clear-cut decision concerning their establishment.

The CHAIRMAN suggested that the Director-General be asked to submit to the Health Assembly the summary records of the discussion on the subject, together with his report.

It was so agreed. (See summary record of the fourteenth meeting, section 6.)

2. PHARMACEUTICAL ADVERTISING: Item 2.6.2 of the Agenda (Resolution WHA20.35; Document EB41/37 and Corr.1)

Dr BERNARD, Assistant Director-General, introducing the document, said that as was stated on page 2, the Director-General was submitting an outline which would be developed for presentation to the Twenty-first World Health Assembly. The annex to the document, containing a draft outline of principles for pharmaceutical advertising, comprised two sections, dealing with advertising to the public and advertising to the medical and related professions, respectively.

The principles had been prepared on the basis, inter alia, of a study published in 1961 of the regulations applied to the advertising of pharmaceutical products in twenty-two countries. The Director-General was endeavouring to bring that study up to date and it was hoped that the work would be completed during the current year.

Professor AUJALEU said that some of the principles included in the annex applied to both advertising to the public and advertising to the profession. He suggested that the common principles be stated first and those applicable to only one or the other sectors be listed accordingly.

Professor MACUCH said that the question of advertising was closely linked with that of the pharmaceutical and clinical tests that were or should be applied to medicaments. Legislation covering such tests had been introduced in certain countries and it was eminently desirable that similar laws should be enacted in all countries. If only true information could be given in advertisements about medicines freely sold to the public, the advertising of ineffectual or noxious preparations would be automatically ruled out. The large sales obtained through the advertising of habit-forming drugs or medicines was a particularly dangerous aspect of the problem. In the case of advertising to the profession, care should be taken to avoid exaggerating the efficacy of the product advertised, while any undesirable reactions that might be provoked and could even prevent a cure should be indicated.

Some countries had adopted the wise precaution of permitting the advertising of medicaments only in professional publications, and exclusively of remedies whose production or importation had been authorized.

Dr OTOLORIN suggested that the first section in the annex should include a reference to the use of ambiguity in the wording of advertisements, a practice applied with great skill by certain advertisers, particularly in the translation of advertisements for popular remedies.

Dr POPESCO, alternate to Professor Moraru, observed that it would be to the advantage of everyone concerned if some of the money and intelligence used in advertising could be applied to the development of simple and effective controls. Advertising for the profession could assist the practitioner in making a judicious choice among the ever-growing number of pharmaceutical preparations launched on the market. While he agreed with the principles formulated in the annex to the document, he wondered whether advertisements for medicaments should not state whether or not the product in question had been submitted to an official test.

Professor von MANGER-KOENIG said he assumed that the Secretariat in studying the question of scientific criteria was taking into account relevant documents produced by organizations such as the European Economic Community and the European Free Trade Association. In the formulation of the criteria to be adopted, the greatest difficulty would be in striking a balance between the general principles and the detailed regulations, in order to ensure the acceptance of the criteria put forward.

Dr BADAROU said that while advertising for the profession could serve a useful informative function, advertising for the promotion of sales could not be regarded as beneficial to public health. It tended rather to make sick people spend money without being sure whether the medicines they bought would cure them. For example, aspirin, and similar preparations, advertised as the remedy for all kinds of pain, in point of fact seldom removed the cause of the pain. It was, in reality, very unfortunate that advertising of that type was tolerated. He fully appreciated the fact that the commercial interests involved made the question of such advertising a delicate one; nevertheless, he wondered whether it should not be studied with a view to seeing whether the defects of the system were really beyond remedy.

Dr ENGEL said he would like to know whether the principles annexed to the report related only to the advertising of products covered by the Organization's traditional definition of drugs, or whether they would cover non-registered products such as preparations sold for nutritional purposes, vitamins and tonics.

Dr MARTÍNEZ suggested that the Secretariat follow up the preparation of its draft outline of principles by considering whether governments should be approached with a view to impressing on them the need for adequate legislation on the advertising of medical products. He presumed that all members were agreed on the principle that the right to advertise drugs should be subject to limitation by law, and many countries no doubt had the necessary legislation on their statute books; at the same time, it might be possible and desirable to suggest to the others that they pass the necessary law.

Dr OLGUÍN said that the comments he had made earlier in the debate on the responsibility of States for the quality of the drugs produced in their countries applied also to the question of the advertising and distribution of drugs. The latter responsibility was covered by the document in respect of advertising both to the public and to the profession. In advertisements to the profession, the information supplied should be based on scientifically determined concrete facts.

The advertising of medicaments sold freely to the public should be restricted to authorized products, excluding drugs dispensed only on medical prescription. Furthermore, the advertising of such authorized products should indicate their pharmacological action, described in such a way that it would not encourage self-medication or excesses that might be prejudicial to public health or professional ethics.

He shared the views of Dr Martínez that all countries should have adequate legislation for the control of the advertising and distribution of drugs.

Dr HALBACH, Director, Division of Pharmacology and Toxicology, replying to Dr Engel's question about preparations such as tonics and vitamins, said that the Assembly resolution had explicitly referred to drugs, and the criteria in the document made a distinction between

prescription and non-prescription drugs. Any attempt to extend those criteria to non-registered products would raise problems involving other organizations and institutions. The question was, however, important and should not be lost sight of.

Dr BERNARD observed that since the document was only a progress report, the points raised by Dr Aujaleu and Dr Otolorin could be incorporated in the final report. Although in its present form the report dealt only with drugs, if it were at any time considered desirable to extend its scope to cover other products, the Secretariat would certainly extend it.

Dr ENGEL said that he had not suggested that the question of advertising non-registered preparations be included in the report at that stage. He had only wished to draw the attention of the Board to the very serious issues raised by such preparations. In his opinion, there was no possibility of taking action in the matter in the existing situation. At the same time, he would be glad to have a clearer definition of the term "drugs".

Dr BADAROU asked whether the Board could not recommend the prohibition of the advertising of pharmaceutical products to the public, for such advertising only encouraged the public to consume ever larger quantities of medicines which did not in his opinion improve the peoples' health.

Dr OTOLORIN said that the legal prohibition of such advertising would not have the desired effect, since it would only lead to the imposition of the penalty after the product had been advertised and the damage therefore done. He suggested that the Director-General consider the question further in his final report.

Professor MACÚCH read out the following draft resolution:

The Executive Board,

Considering the constant and rapid increase in the number of pharmaceutical preparations available on the market;

Noting that in certain cases drugs have been excessively advertised without having undergone the necessary experimental and clinical evaluation which frequently gives rise in the public to unjustified hopes;

Recognizing that such information in the press on new pharmaceutical preparations if not objective may be detrimental to the public; and

Recalling the resolution WHA20.35,

1. NOTES with appreciation the Director-General's report on the ethical and scientific criteria that from the medical point of view should govern the advertising of drugs; and

2. REQUESTS the Director-General to prepare for the Twenty-first World Health Assembly on the basis of the draft outline of "Principles for Pharmaceutical Advertising" a report together with any recommendations he may deem appropriate, taking into account the discussions on the subject at the forty-first session of the Board.

Dr OTOLORIN, Rapporteur, observed that the developing countries suffered from the form taken by the advertising of existing as well as of new drugs. Accordingly, he proposed that the words "noting that inaccurate claims have been made for drugs" be added to the preamble.

Professor AUJALEU said that articles in the press were also a form of advertising and he feared that the words "in the press" in the third preambular paragraph might make it appear that the resolution was contrary to the principle of the freedom of the press.

Dr BENYAKHLEF drew the attention of the Board to the fact that the word "press" in the third preambular paragraph could refer either to the specialized medical press or to the press in general. In the first case, the public did not read and was not interested in the information conveyed; if that were the interpretation intended, it should be clearly indicated.

The CHAIRMAN suggested that the Rapporteurs prepare a revised text of the draft resolution for submission to the Board.

It was so agreed. (See summary record of the thirteenth meeting, section 7.)

3. HEALTH PROBLEMS OF SEAFARERS AND HEALTH SERVICES AVAILABLE TO THEM: Item 2.7 of the Agenda (Document EB41/10)

Dr KAREFA-SMART, Assistant Director-General, introducing the item, said that after the Nineteenth World Health Assembly the Director-General had sent out a circular letter to all governments inviting them to make the necessary specialized medical care available for seafarers. He had also engaged a consultant to assist in studying the possibility of establishing pilot health centres for seafarers. The Secretariat had not yet completed its study of the findings of the consultant, with the financial implications. The Director-General could only submit at the present time a further progress report to the Board. A fuller report would be presented to the Twenty-first World Health Assembly.

Dr OTOLORIN asked why Nigeria was not included among the countries listed in the first paragraph on page 2 of document EB41/10.

Dr KAREFA-SMART said that Nigeria had in fact expressed an interest in having a pilot health centre. Conditions in Nigeria had prevented the consultant from visiting that country. The list of countries on page 2 was not meant to be complete, and the port of Lagos would be visited in due course.

Dr TOTTIE, alternate to Dr Engel, suggested that the Organization, perhaps in collaboration with the ILO, undertake a study of the possible consequences of the changed conditions in seafaring life that would come about with the introduction of ships of up to 200 000 or 500 000 tons.

The CHAIRMAN suggested that the following draft resolution be adopted:

The Executive Board,

Having considered the report of the Director-General on the health problems of seafarers and health services available to them,

1. NOTES the report; and

2. REQUESTS the Director-General to bring this report up to date for presentation to the Twenty-first World Health Assembly.

Decision: The draft resolution was adopted.[1]

The meeting rose at 12.35 p.m.

[1] Resolution EB41.R17.