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UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION
Vienna International Centre, P.O. Box 300, 1400 Vienna, Austria
Tel: (+43-1) 26026-0 · www.unido.org · unido@unido.org

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QUALITY CONTROL IN PHARMACEUTICAL MANUFACTURE 1/

presented by the

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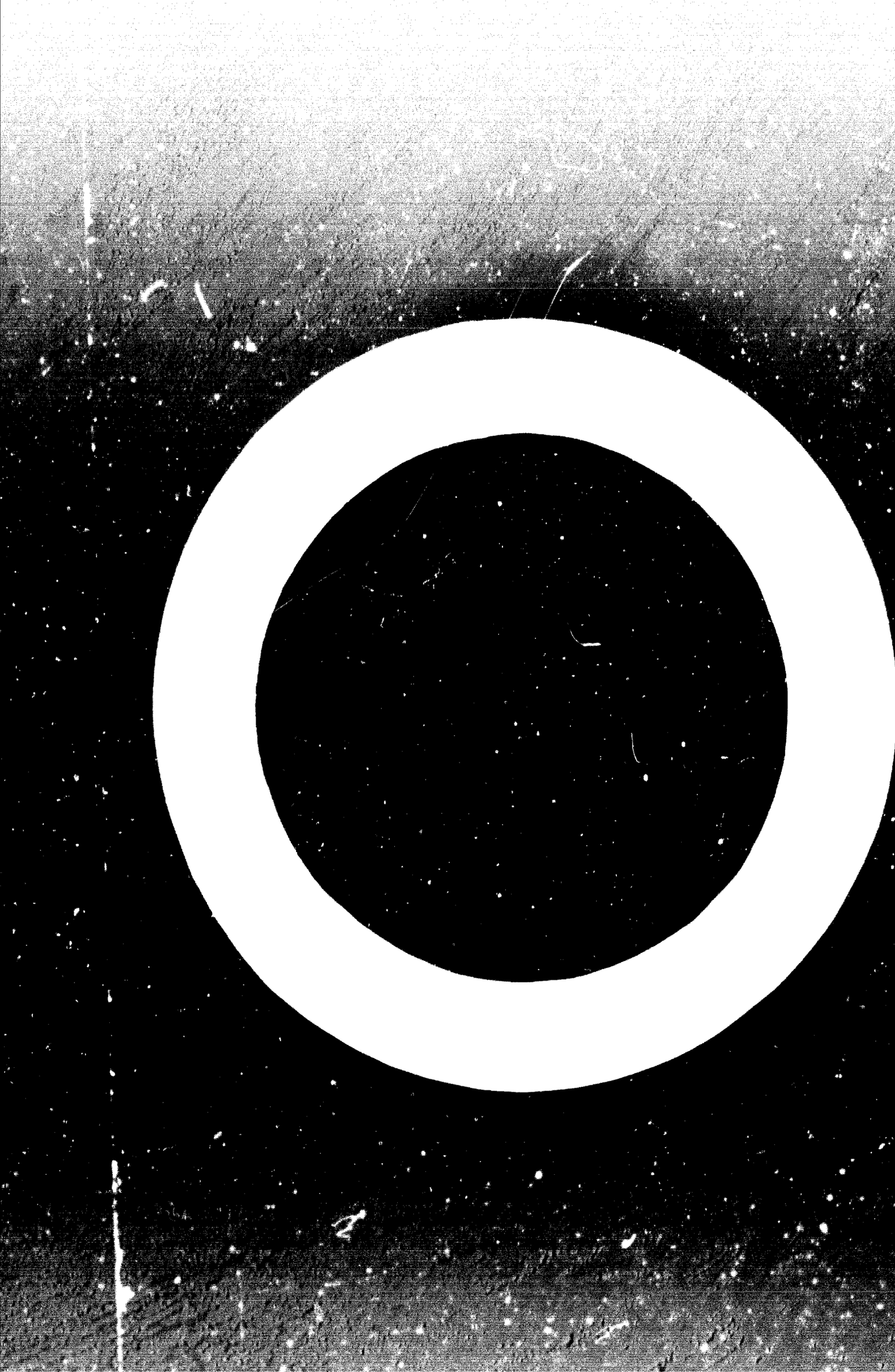

The following is an attempt to give a review of the activities of WHO in the field of pharmaceutical quality control and special attention will be paid to control in manufacturing establishments.

It is first necessary to define the scope of pharmaceutical quality control.

The suitability of drugs for their intended use, is determined by two groups of factors:

1. efficacy weighed against safety to health and
2. conformity to its specifications regarding identity, strength, purity and other relevant characteristics.

Efficacy and safety of drugs have already been discussed earlier this week and will only be mentioned here that in order to assure reproducibility of efficacy and safety it is essential to establish adequate specifications for the drugs and their dosage forms. In fact, once the efficacy and safety have been established, the quality of drugs available in commerce is judged by measuring identity, strength, purity and other relevant characteristics.

Quality control is practised to achieve sustained and uniform manufacture of products of desired quality levels. The essential factors in this respect are:

(a) product quality specifications and

(b) production control.

Product quality specifications are necessary to determine suitability for use in manufacture of starting materials, and to determine the quality of end products.

Specifications for starting materials are based on the characteristics of processes used for the production of these materials and consist usually of -

(a) specific identification tests;

(b) purity tests;

(c) assay method;

(d) physical characteristics.

These specifications are usually found in official compendia, such as pharmacopoeias, codices and formularies.

Specifications for finished products are the established specifications for the finished drugs which must provide all criteria necessary to determine their acceptability.

Specifications for "half-finished" products are mainly of interest for the manufacturer in order to determine either the suitability of such products for further processing or the acceptability of products if they are procured from outside sources.

The second, and perhaps the most important aspect of quality control of drugs in their dosage form, is the production control.

There are three main aspects of production control. Firstly, the suitability of manufacturing premises and equipment and the availability of competent staff. Secondly, process control to ascertain that the established production procedure is followed and that no mix-ups and contaminations occur, and thirdly final control of the end products to ensure that they comply with the established specifications.

The activities of WHO in the field of pharmaceutical quality control have, from the very beginning, been concentrated on the establishment of quality control specifications, and it is only during the last few years that the production control aspect has been brought into the foreground.

Product quality specifications

The work on quality control specifications within the WHO programme has resulted in two editions of the International Pharmacopoeia. It may be of interest to outline briefly the history of this work.

In accordance with resolutions of the First and Third World Health Assemblies (1947 and 1950), the Organization, with the aid of qualified experts, began to compile an International Pharmacopoeia which would set down the most useful and modern specifications for drugs in world-wide use. This work resulted in the publication of the First Edition of the International Pharmacopoeia in 1951, followed by the publication of Volume II in 1955, and of a Supplement in 1959.

Specifications for reagents

During the work on the First Edition of the International Pharmacopoeia it was felt that more detailed specifications for reagents used in connection with the assays and tests included therein should be drawn up.

A working group was organized and the work on specifications for reagents, based on existing specifications and on collaborative work of experts was later co-ordinated with the preparation of the Second Edition of the International Pharmacopoeia.

In 1958 draft specifications for [illegible] were available and were widely circulated for comments, which [illegible] 1959

consideration in the preparation of the final text. In accordance with the recommendations in the Seventeenth Report of the Expert Committee some instrumental methods such as flame photometry were included as alternatives to older methods. The "Specifications for reagents mentioned in the International Pharmacopoeia" were published in English (1966) and in French (1966).

The specifications included in this volume also apply to the reagents required for the tests and assays of drugs described in the Second Edition of the International Pharmacopoeia and are quoted in the list of reagents and test solutions in that volume.

Second Edition of the International Pharmacopoeia

The WHO Expert Committee on the International Pharmacopoeia recommended in 1965 that the First Edition of the International Pharmacopoeia should be revised so as to delete the tests and to revise the general methods of testing as may be necessary to keep them in line with developments in pharmaceutical analysis.

Before deciding on the content of the Second Edition advice was invited from the World Medical Association, the International Pharmaceutical Federation, members of the Expert Advisory Panel, and other specialists.

During the session of the Expert Committee held in Geneva in November 1966, a preliminary list of contents of the Second Edition was compiled and, after further consultations, the final list established.

Specifications for 160 newer drugs are to be introduced in the Second Edition, while 110 monographs of the First Edition were omitted, to give a total of 345 drug entries with 40 monographs. The text was prepared [illegible]

number of other specialists from different countries. The analytical procedures given in the monograms and appendices have been tested in the laboratories of national pharmacopoeias, in national laboratories for pharmaceutical quality control, in the laboratories of a number of manufacturing firms, and in pharmaceutical and other institutions.

Modern analytical methods used in pharmaceutical quality control are described in the appendices; for example, infra-red spectrophotometry, polarography, chromatography (column, paper and thin-layer), radioactivity, non-aqueous titration, and determination of melting-range and melting-point and identification of substances by the Kofler method.

A provisional text of the Second Edition was sent on 9 March 1964 to members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and a number of other specialists interested in this work, with a covering letter, asking for comments, which were later considered for possible incorporation in the provisional text.

In October 1964, the revised provisional text was forwarded to Member and Associate Member States, inviting them to submit comments within three months.

These and further comments were integrated in the text of the Second Edition in order to make it to its requirements.

The title "International Pharmacopoeia" dates from a period when it still seemed possible to assemble under an international authority a collection of specifications that could be adopted by national authorities. Today this is possible only in part, and the second edition of the International Pharmacopoeia was published in 1967 under the main title "Specifications for the quality control of pharmaceuticals".

It is a collection of recommended specifications which are not intended to have legal status as such in any country, but are offered as reference for the establishment of specifications.

Chemical Reference Substances

Spectrophotometric assays and identification tests, as well as paper and thin-layer chromatographic purity tests, applied in the International Pharmacopoeia, require the use of chemical reference substances. WHO provides a number of International Chemical Reference Substances which are established upon the advice of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. The characteristics of the substances selected are determined by the WHO Centre for Chemical Reference Substances in Solna, Sweden, in collaboration with specialists designated by WHO.

At present, about 40 substances are available from the Centre, mainly steroids, cardiac glucosides, semi-synthetic penicillins and a few other substances.

There is little doubt that reference substances will be increasingly used in quality control of drugs in the future, and the Centre invites the close collaboration of all national authorities concerned with the establishment of chemical reference substances. By these means, it is hoped to achieve uniformity and, as far as possible, actual identity in the reference substances that are established.

Future work on specifications

The present way of compiling the International Pharmacopoeia has been criticized from important viewpoints which also, to a certain extent, apply to many national pharmacopoeias:

(1) the time between new editions is too long in relation to the speed with which new drugs are introduced into the market and

(2) there is a tendency to conservatism in the sense that technically simple but little selective methods are sometimes described.

In 1967 the World Health Assembly, in a resolution, requested the Director-General to continue work on analytical control specifications for international acceptance to be published as they are completed".

The WHO Expert Committee on Specifications for Pharmaceutical Preparations, in its 22nd report which is now in print, suggests for further discussion a procedure for the early provision of drug specifications which would be established in co-operation between national control authorities, manufacturers and WHO.

International Nonproprietary Names for Pharmaceutical Substances

In order to avoid the confusion which arises when different nonproprietary names are used for the same substances, WHO has operated since 1952 a programme for the establishment of international nonproprietary names. Requests for international nonproprietary names are received from national authorities, manufacturers and other interested persons, and the proposed international nonproprietary names are selected in accordance with the Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances and the General Principles for Guidance in Devising International Nonproprietary Names for Pharmaceutical Substances.

Lists of new proposed international nonproprietary names are published at present twice a year in the WHO Chronicle and annexed to the lists are details of the Procedure and General Principles followed in selecting the names. A Cumulative list of international nonproprietary names is available.

International nonproprietary names are used in the titles of monographs and in the text of the Second Edition of the International Pharmacopoeia and in many national pharmacopoeias. They are also widely used throughout the world for regulatory, labelling, scientific and other purposes.

National nomenclature commissions exist in a growing number of Member States, and it is now the practice of many manufacturers to request through these national nomenclature commissions the selection of an international nonproprietary name at about the time that a new drug is placed on the market. By this early action it should be possible to ensure that the same nonproprietary name is used in the labelling of preparations and in the pharmaceutical and medical literature throughout the world.

Good Practices in the Manufacture and Quality Control of Drugs

It was pointed out earlier that within the WHO programme on quality control of drugs the work on requirements for production control is of a more recent date.

The question of quality of drugs moving in international trade has been on the agenda of the World Health Assembly for several years and the Twentieth World Health Assembly (1967), in a resolution, requested the Director-General inter alia "to formulate as soon as possible principles for quality control procedures such as should be incorporated in good drug manufacturing practice".

In August 1967 a WHO group of specialists met in Geneva to assist in the preparation of a set of principles and requirements for good practices in the manufacture and quality control of drugs. The draft text was sent to all Member States of WHO for comments and it was also discussed at a meeting of the Executive Board and the World Health Assembly in 1968. All comments received were considered by an Expert Committee which met in Geneva in October 1968. The report is now in print

As good quality cannot be tested or inspected into products, the desired quality of the final dosage form must be built into the product from the very beginning of the manufacture.

In most cases it is possible to draw up specifications for raw materials which guarantee a satisfactory quality, but in the case of simple pharmaceutical forms such as tablets, although in most instances it is possible to determine that they meet the requirements for activity, it is a very complicated task to prove that raw material is of required purity when it is in the [illegible].

It is of course theoretically possible, using modern analytical methodology, to elaborate purity tests which ensure that the starting materials comply with established specifications, but it would hardly be feasible in practice.

Difficulties arise with the quality control of simple pharmaceutical forms described in pharmacopoeias even if the nature and amount of excipients and diluents are known. It is easy to appreciate the difficulties in drawing up finished product specifications for pharmaceutical forms when such details are not known.

We have to face the fact that finished product specifications alone are of restricted value, unless it can be ascertained that the drug has been manufactured under satisfactory conditions.

The drug manufacturer must assume the responsibility for the quality of his product and he is naturally in the best position to prevent mistakes by exercising adequate care in the various manufacturing procedures.

The production control must be adequate to assure the drug's purity and efficacy. The field of controls in drug production has become as large and actually, at least in some phases, more complex than the production of the drugs themselves.

It is thus evident that the responsibility for quality of drugs must be divided between the drug manufacturers and the official control authorities.

Before discussing the main points of the document on Good Practices in the Manufacture and Quality Control of Drugs it is important to recall that these recommended requirements constitute only a guide and framework which need to be adapted to meet the actual need by the people who actually have to carry out manufacturing procedures. The requirements should be used with discretion and the experts of the firms should be

given the opportunity to check the suitability of any requirements against their individual needs. It should also be pointed out that a document of this kind can never be final; it will have to be continually reviewed and, whenever necessary, revised.

After the first paragraphs of the document, General Considerations and Definitions, follows a section Personnel. This is an important part of the document, especially as the requirement of scientifically trained experts is exceptionally high in the drug industry.

The professional staff responsible for passing expert judgment on specifications, manufacturing procedures and control measures must have a solid scientific background and adequate practical experience in the manufacture and control of drugs. An important consideration is that the formation of such staff in each particular country will depend on the educational facilities available.

The following two paragraphs of the document describe the requirements for Premises and Equipment. Special attention has been given to describing the conditions for minimizing the risk of human errors which could result in faulty formulation, contamination or a mix-up of drugs or auxiliary materials used in the production processes. Written instructions should be given for the cleaning of equipment and it is pointed out that adequate records of such procedures should be maintained.

In the following sections directions for Sanitation, Starting Material and Manufacturing operations are given. The availability of written instructions for the manufacturing procedures and batch manufacturing records are vital to assure the sustained production of products of a consistently high quality and the document therefore gives rather detailed indications. The batch manufacturing records should give the complete manufacturing history of each batch.

In the section labelling and packaging rather stringent directions a[re] iven for the han[dl]ing of labels. The reason is of course that [i]s a crucial phase in the manufacturing process where mistakes very [c]ccur.

[T]he importance of the existence of a quality control department [t]functions autonomously in its sphere of responsibility is stressed [i]n following paragraph and its responsibilities are described in [p]. 3.

[T]he document further conteins a suggestion that it may be advisable [f]or a firm to designate an inspector who regularly surveys the [m]anufacturing and control operations.

[F]inally, recommendations are given for maintaining records of the [d]istribution of drugs and of complaints and adverse reactions reports.

[I]nspection of drug manufacturing establishments by the national [c]ontrol authority is being introduced in an increasing number of [c]ountries. The national control authorities must then have at their [d]isposal laboratory facilities of a high standard and adequately educated [a]nd trained experts to perform these duties.

[I]t appears to be a realistic approach to achieving a sustained and [h]igh manufacture of drugs of a defined quality if the responsibility [f]or the quality control is shared between the manufacturers and the [n]ational control authorities.


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