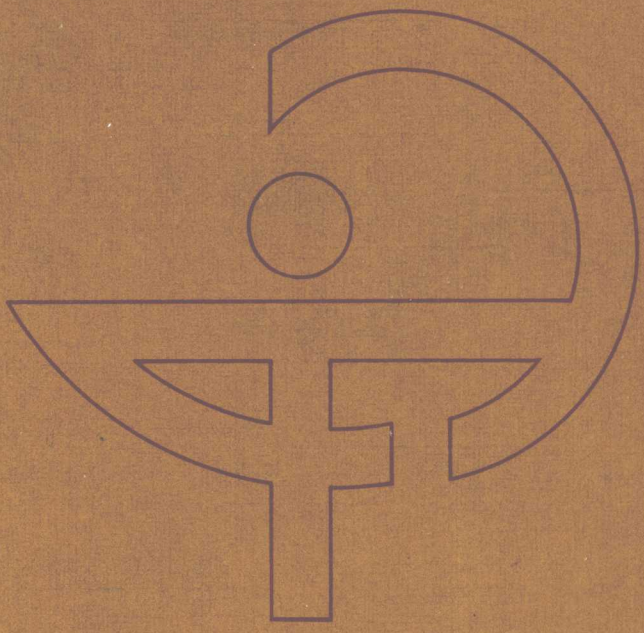
The Quality Control of Medicines

P. B. DEASY & R. F. TIMONEY
editors



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INTRODUCTION

The 35th International Congress of Pharmaceutical Sciences organized by the Pharmaceutical Society of Ireland on behalf of the Federation Internationale Pharmaceutique was held in Dublin, 1—5 September 1975. The theme chosen for the Congress was "the basis for the quality control of medicines", because of the importance and relevance of quality control in the production and distribution of medicines at national and international levels. Some 1700 people from all over the world attended the Congress. It was decided to publish in full the major papers presented at the Congress because of the very great interest shown in the proceedings of the Congress by those attending and by many others unable to attend.

This book is arranged to conform with the manner in which the theme of the Congress was developed by the eminent invited speakers. Following the inaugural address a main symposium was held where five speakers presented a review of the quality control of medicines under the general headings of (i) chemical and physical aspects, (ii) biological aspects, (iii) control of drug delivery systems, (iv) storage problems and (v) problems of international control.

Certain aspects of the content of the main symposium were then developed in greater depth in parallel symposia. In the first parallel symposium some novel physicochemical aspects of the quality control of medicines were treated under the headings of spectrofluorimetry, mass spectrometry, detection in gas chromatography and automation in pharmaceutical analysis. The second parallel symposium developed certain microbiological aspects of quality control under the headings of sterility testing and microbiological control of non-sterile products and ophthalmic preparations. Under the title bioavailability testing, the third parallel symposium dealt with advances in pharmacokinetics, pharmacological and clinical measurements, analytical problems of in vitro and in vivo correlations and problems in the design of monographs on bioavailability. Certain separation techniques such as ion pair and complex extraction, determination of impurities by thin-layer chroma-

tography, spectroscopic determination in the presence of degradation products and adsorption problems in chromatography were treated in the fourth parallel symposium. The final symposium on submissions to regulatory bodies and international aspects of drug control covered aspects of politics in submissions, regulatory problems in small countries and various pharmacopoeial problems. In addition to the contributions of the invited speakers, approximately 250 related personal communications were presented at the Congress, which are not included in this book.

The Scientific Programme Committee made every effort to minimize duplication of subject matter in the contributions of the various speakers. However, a certain amount of overlap was unavoidable because of the manner in which the main and parallel symposia were developed and interrelated, and because of the many contributors involved. The original papers of Marignan, Dony, Lesne, Pesez and Lalanne were in French and those of Richter, Rücker and Kubin were in German. All these contributions have been translated into English as literally as possible.

Finally, as editors we would like to thank the contributors for their cooperation in the publication of this book.

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INAUGURAL ADDRESS

THE QUALITY CONTROL OF MEDICINES: A NATIONAL AND INTERNATIONAL RESPONSIBILITY

R.F. TIMONEY

The theme of the 35th International Congress of Pharmaceutical Sciences is most appropriate in recognition of the importance at national and international levels of quality control of medicines by the development and application of specialized scientific techniques at all stages of manufacture and by the increasing trend towards the use of suitable legislation to ensure compliance with national specifications by manufacturers and suppliers of medicines. It is also appropriate at this meeting to record that the International Pharmaceutical Federation took an active part in initiating the developments towards the improvement of quality standards for pharmaceutical preparations in 1947, and subsequently, through the meetings of directors of laboratories for the control of medicines.

During the past two decades the pharmaceutical industry throughout the world has provided a vast range of new, specific drugs for human use and has evolved an increasing sophistication in the production of formulated products, thus contributing to higher standards of health in most countries than in any previous age. The need for precisely-defined and acceptable specifications for production control during manufacturing processes and for the final products, in order to assure reproducibility in the wide context of drug safety is recognized, not only by the pharmaceutical industry but also by national drug regulatory bodies and international organizations actively concerned with the quality of medicines moving in international commerce. The primary responsibility for assuring quality control of medicines is that of the manufacturer. However, it is recognized in most countries that the national health authorities must exercise comprehensive surveillance by legislative methods over pharmaceutical manufacturers within their jurisdiction, in order to ensure observance of good manufacturing practices and quality control of the products. The trends towards the removal of obstacles in international commerce, providing, inter alia, for freer movement of medicines, has concerned international bodies, including the World Health Organization, in the problems of assuring quality control of medicines on a global basis.

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THE WORLD HEALTH ORGANIZATION AND QUALITY CONTROL IN THE PRODUCTION OF MEDICINES

Since its inception the World Health Organization has actively promoted the exchange of scientific data on the subject of quality control in the production of medicines. Expert Committees organized by WHO have produced reports on the Quality Control of Pharmaceutical Preparations in which recommended practices for the manufacture and quality control of drugs are outlined. Among the procedures considered in these reports are the organization of a national control authority as an agency for quality control, inspection and laboratory services, problems relating to good manufacturing practices, their enforcement and the coordination of regulations at the international level.

The twenty-second report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations contains the following statement:

> "In 1967, the Twentieth World Health Assembly requested the Director-General to take a number of measures to assist Member States in their efforts to improve the quality control of drugs. In particular, it called for the formulation, as soon as possible, of principles for quality control procedures that should be applied to drug manufacturing practice."

Subsequently, a document entitled "Draft Requirements for Good Manufacturing Practice in the Manufacture and Quality Control of Drugs and Pharmaceutical Specialities" was submitted to and favourably received by the 21st World Health Assembly.

The Twenty-Second World Health Assembly in 1969 recommended that Member States should adopt and apply (1) the requirements for "Good Practices in the Manufacture and Quality Control of Drugs" and (2) a "Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce". In response to a request from the Twenty-Third World Health Assembly, the Expert Committee on Specifications for Pharmaceutical Preparations undertook a review of comments on both documents from a number of Member States, and, on the basis of the comments proposed revised texts which were sent to all Member States for further comments in January 1974. The twenty-fifth report of the Committee, which was published this year, contains amended versions of the two documents incorporating recommendations based on submissions from Member States. Although these recommendations are not mandatory, they have been accepted as useful guidelines by national authorities in the development of legislative procedures for assurance of the quality control of drugs.

The publication of an International Pharmacopoeia is a further valuable contribution by WHO in the field of pharmaceutical quality control. The specifications are not intended to have legal status per se, and any Member State may include all or part of the provisions in its national requirements. The title for the second edition (published in 1967); 'Specifications for the

Quality Control of Pharmaceutical Preparations', clearly emphasizes the purpose of the monograph specifications in a modern pharmacopoeia.

REGIONAL INTERNATIONAL ORGANIZATIONS AND QUALITY CONTROL

Several regional or supra-national organizations are also actively concerned with the problem of achieving quality assurance of medicines in the wider context of eliminating trade and other barriers to ensure greater economic and social progress within the countries of these regions.

A Council Directive of the European Economic Community (EEC) (no. 65/65 of January 1965) specified the provisions for proprietary midicinal products which must be satisfied prior to authorization by the competent authority of a Member State of the EEC. The aim of this directive is to pave the way for the eventual free movement of proprietary medicines within the European Economic Community. Applications for authorization by a pharmaceutical manufacturer must be accompanied by specified information about the products, including the method of formulation, therapeutic indications, contra-indications and quality control. The latter includes control tests of the constituents of the formulation before use in the manufacture of the dosage-form, in-process controls, analysis of the finished product, and stability tests to demonstrate compliance of the product with the appropriate specifications throughout the stated shelf life under normal or specified storage conditions. Agreement was reached early this year by the EEC Council of Ministers on the enlargement of this directive, to include full quality standards and the measures needed to comply with the provisions must be enforced by Member States within eighteen months of its notification. In Ireland, the European Communities (Proprietary Medicinal Products) Regulations, 1974, have been introduced which give statutory effect to the provisions of EEC Directive 65/65, to products coming on the market for the first time after the 1st of October, 1974. Labelling provisions in the directive will not apply until after the 1st of October, 1975, due to practical problems posed for the industry. The provisions of the directive will be extended to products on the market before the 1st of October, 1974 by further regulations.

A further directive agreed by the Council of Ministers sets out in detail the data on chemistry, pharmacy, pharmacology, toxicity and clinical trials that Member States should require in support of applications for product licences. The purpose of this directive is to ensure that adoption of the same standards and protocols by all Member States will enable the competent authorities in each state to make their decisions regarding authorization on the basis of uniform tests and by reference to uniform criteria, and thus avoid differences in evaluation. In practice, the recommended procedures outlined in this directive have already been enforced or implemented on a voluntary basis by drug regulatory bodies in most, if not all, of the EEC countries.

EUROPEAN FREE TRADE ASSOCIATION (EFTA)

In contrast to the supranational legislative competence of the EEC, there is no legislation on any of the activities in which the European Free Trade Association (EFTA) is engaged. A Convention for the Mutual Recognition of Inspections concerning the Manufacture of Pharmaceutical Products was agreed upon by EFTA member states in October 1970, and has since been ratified by all the member states.

Fundamentally, the Convention provides that an inspection carried out by one national authority shall, where certain conditions are fulfilled, be regarded by the national authority of the importing country as being made by its own inspectorate. It is concerned, therefore, with quality control of pharmaceutical products irrespective of whether information on such control is required in the course of the registration procedure or not. Article 2 of the Convention relates to information which may be requested by the competent authority of an importing Contracting State. Such information may concern either the general standards of manufacturing practice, or specific standards of manufacture or quality control in respect of particular products or both. Supplementary questions can be asked by the requesting competent authority which are relevant to the quality control of pharmaceutical products and based on the legal provisions of the importing Contracting State. Workshops, arranged by the national inspectorate of one country for the inspectors of the other national authorities, have been held on areas of interest, e.g. the manufacturing of sterile products, and have proved a valuable means of familiarization with standards of good manufacturing practice, while simultaneously contributing to the mutual training of inspectors.

THE ROLE OF PHARMACOPOEIAS

Reference has been made earlier in this address to the valuable contribution of the International Pharmacopoeia in providing recommended specifications for the quality control of pharmaceutical preparations. Regional pharmacopoeias and compendia are now playing an increasingly important role in providing guidance on the quality control of drugs, adjuvants and pharmaceutical formulations, and in the reference substances in pharmacopoeial specifications for various procedures. The Nordic Pharmacopoeia, the longest-established of the regional pharmacopoeias, is designed to provide methods of analysis and specifications for the manufacturer of pharmaceutical products. The European Pharmacopoeia, which was established by the European Pharmacopoeia Convention in 1964 by the participating countries of the Partial Agreement in the Council of Europe, is being progressively developed in accordance with the provisions of the Convention; its requirements are legally binding in those countries signatory to the Convention. The publication

since 1969 of two volumes of the European Pharmacopoeia, with a third volume due to be published later this year, is a notable achievement in a specialized field despite difficulties due to different traditions and industrial practices in the countries concerned. The Compendium Medicamentorium provides recommendations for the standards of quality of pharmaceutical products within the framework of the Council for Mutual Economic Aid (Comecon), although as yet the specifications are not obligatory. National pharmacopoeias continue to contribute to the control of quality standards of products in accepted use within the countries in which they operate. The pharmaceutical industry could utilize pharmacopoeial standards to a greater extent if there was a wider acceptance by national authorities of the specifications of regional pharmacopoeias and if the latter could be revised at more frequent intervals.

THE PHARMACEUTICAL INDUSTRY

The positive contributions of the pharmaceutical industry throughout the world to the significant advances which have been made, particularly within the last decade, towards the attainment of good manufacturing practice and the quality control of medicines, deserve due acknowledgement and tribute in the context of the subject of this address. The development of suitable facilities and procedures for the technical operations involved in the provision of good manufacturing practices and the detailed organization of administration to ensure the maintenance of high standards throughout the whole process of manufacture, have evolved largely through the initiative and ingenuity of the pharmaceutical industry. The principle and application of self-regulation is a measure of the recognition by the industry of its responsibilities in ensuring high standards in the safety and quality of medicines. Much of the progress which has been achieved in the development of new and more specific physicochemical and biological methods for evaluation of drugs and pharmaceutical products, detection of trace amounts of impurities, the introduction of 'drug-delivery' systems and prediction of storage time, has been due to the efforts of research and development scientists within the pharmaceutical industries. During this Congress we will have the privilege of hearing scientific experts from pharmaceutical companies in many countries presenting papers on a wide range of analytical and testing procedures used in the quality control of medicines.

National associations of pharmaceutical manufacturers exist in most countries and they are concerned, inter alia, with research and development, methods of production and quality control. On the international level, federal associations of pharmaceutical industries exist in the EEC countries (Groupement International de l'Industrie Pharmaceutique (G11P)), the EFTA group (Pharmaceutical Industries' Association (PIA)) and in Latin America (FIFARMA).