British Pharmacopœia 1980

Volume I

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Medicines Commission
pursuant to the Medicines Act 1968

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Notice

Patents

In this Pharmacopœia certain drugs and preparations have been included notwithstanding the existence of actual or potential patent rights. In so far as such substances are protected by Letters Patent their inclusion in this Pharmacopœia neither conveys, nor implies, licence to manufacture.

Preface

The British Pharmacopœia 1980 is published by Her Majesty's Stationery Office for the Health Ministers on the recommendation of the Medicines Commission in accordance with section 99(6) of the Medicines Act 1968.

This is the first edition of the Pharmacopœia that has been prepared wholly under the provisions of the Medicines Act, a fact that is reflected in its greatly enlarged scope. Complete, edited texts of the European Pharmacopœia requirements for many materials are included in fulfilment of the terms of the Convention on the Elaboration of a European Pharmacopœia (Treaty Series No. 32: 1974). In addition, monographs for many materials that were formerly described in the British Pharmaceutical Codex have been included in accordance with an agreement reached between the Medicines Commission and the Pharmaceutical Society of Great Britain whereby after 1978 official standards for medicinal products will be provided only in the British Pharmacopœia.

The Medicines Commission believes that the role of the Pharmacopœia in providing publicly available standards that apply to a product at any time during its shelf-life is of considerable value in safeguarding purchasers and users of medicinal products. The provisions of section 65 of the Medicines Act 1968 relating to the compliance of products with standards specified in monographs of the Pharmacopœia may be used to supplement those of section 64 which prohibit the sale or the supply on prescription, to the prejudice of the purchaser, of any medicinal product which is not of the nature or quality demanded. The relevance of the publicly available specifications of the British Pharmacopœia in this connection is clear.

The preparation of this greatly enlarged version of the British Pharmacopœia has made very heavy demands on the members of the British Pharmacopœia Commission, its committees and its staff. The Medicines Commission wishes to record appreciation for the services of all who have contributed to this important work. In addition it acknowledges the ready co-operation of the majority of the industrial organisations that have been consulted for information and advice. This willing support has enabled the preparation and publication of the British Pharmacopœia 1980 to be brought to a successful conclusion.

Finally the Medicines Commission record their appreciation of the work carried out by members of the British Pharmacopœia Commission who have recently retired. In particular they acknowledge the outstanding contributions made by Sir Frank Hartley and Dr D. C. Garratt, both of whom have served the British Pharmacopœia Commission in many capacities for more than thirty years, Sir Frank Hartley having been Chairman since 1970. We benefit greatly from their unstinted efforts and wise counsel.

British Pharmacopœia Commission

A new British Pharmacopœia Commission was appointed by the Secretaries of State respectively concerned with health in England, in Wales and in Scotland and the Minister of Health and Social Services for Northern Ireland, acting jointly, in exercise of their powers under section 4 of the Medicines Act 1968, to succeed the Commission formerly established by the General Medical Council.

The duties of the British Pharmacopœia Commission are set out in the Medicines (British Pharmacopœia Commission) Order 1970, in the following manner:

(a) the preparation under section 99(1) of the Act of any new edition of the British Pharmacopœia;

(b) the preparation under section 99(1) of the Act, as given effect by section 102(1) thereof, of any amendments of the edition of the British Pharmacopœia published in 1968 or any new edition of it; and

(c) the preparation under section 100 of the Act (which provides for the preparation and publication of lists of names to be used as headings to monographs in the British Pharmacopœia) of any list of names and the preparation under that section as given effect by section 102(2) of the Act of any amendments of any published list.

Members of the British Pharmacopœia Commission are appointed by the Health Ministers on the recommendation of the Medicines Commission. Appointments are usually for a (renewable) term of four years.

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Membership of the British Pharmacopœia Commission

Chairman

Sir Frank Hartley† CBE, BSC, PHD, FPS, CCHEM, FRIC,
Lately Vice-Chancellor of the University of London.

Vice-Chairman

J. B. Stenlake‡ DSC, PHD, FPS, CCHEM, FRIC, FRSE,
Professor of Pharmacy in the University of Strathclyde.

W. G. Allen‡ MRCVS,
A Veterinary Surgeon.

A. O. Betts† BSC, MA, PHD, MRCVS,
Principal and Dean of the Royal Veterinary College, University of London.

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W. G. Overend‡ PHD, DSC, CCHEM, FRIC,
Master of Birkbeck College and Professor of Chemistry in the University of London.

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of Medicine in the University of Leeds.

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C. A. Johnson, BPHARM, BSC, FPS, CCHEM, FRIC, MPHA.

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* Term of office ended 31 December 1977.
† Term of office ended 31 December 1979.
‡ Term of office ends 31 December 1981.
§ Resigned 31 December 1977.

Membership of Committees and Panels

The Commission appointed the following Committees and Panels to advise it in carrying out its duties. Membership has changed from time to time; the lists given below include all who have served during the period 1973 to 1978.

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COMMITTEE 7: MEDICINAL CHEMICALS (B)

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COMMITTEE 22: EXCIPIENTS

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Introduction

An expanded Pharmacopœia

This edition of the British Pharmacopœia, the thirteenth, differs from earlier editions in important respects, particularly in its treatment of monographs for materials that are now included in the European Pharmacopœia. Section 65(7) of the Medicines Act 1968 gives precedence to monographs in the current edition of the European Pharmacopœia and this has hitherto been acknowledged in the British Pharmacopœia by a simple cross-reference to the European publication accompanied, where appropriate, by additional information of a non-mandatory nature such as an Action and Use statement or an indication of official preparations that contain the material. This practice of cross-reference has given rise to considerable criticism from users of the Pharmacopœia, a criticism that seemed more and more justified as the number of books comprising the current edition of the European Pharmacopœia increased to five (three main volumes and two supplements) and those comprising the British Pharmacopœia to four (the 1973 edition and its three addenda). The British Pharmacopœia Commission provided some alleviation of the problem by including, in the Addendum 1978 to the British Pharmacopœia 1973, a cumulative index that indicated in which of the nine books reference to any given material might be found. The considerable inconvenience of this situation was nevertheless still readily apparent.

To improve matters the British Pharmacopœia Commission has decided that, in so far as is possible, all 'appropriate current monographs' referred to in Section 65(5) of the Act, as modified by Section 65(7), should be included in the British Pharmacopœia. To this end the present edition includes, in detail, the requirements of almost all of the monographs that currently comprise the European Pharmacopœia; a few have been omitted where the material described is considered to be of little relevance to the practice of medicine in the United Kingdom (for example saffron) or where its use has been reported as being undesirable (for example phenacetin). Monographs so included are distinguished by a five-pointed star that is based upon those appearing in the emblem of the Council of Europe. It should be noted that the requirements of such monographs have been presented in an edited and rearranged format in order to effect a style consistent with that used for the national monographs, established by the British Pharmacopœia Commission, which comprise the majority of the entries. An addition to the General Notices of the British Pharmacopœia makes it clear that, in cases of doubt or dispute, reference should be made to the text published under the direction of the Council of Europe (Partial Agreement) in accordance with the Convention on the Elaboration of a European Pharmacopœia. For routine use, however, the British Pharmacopœia Commission is confident that the inclusion of such edited texts in the Pharmacopœia will be welcomed by most users.

As a further step in presenting all appropriate current monographs in the British Pharmacopœia, this edition includes many monographs for materials that were formerly described in the British Pharmaceutical Codex. The task of reviewing and, where necessary, revising all the standards of the BPC 1973 is a formidable one and had not been completed at the time that the BP 1980 was sent to the printer. Monographs of the British Pharmaceutical Codex 1973 and of its Sup-

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plement 1976 continue in force as the 'current monographs' until superseded by entries in either the European or British Pharmacopœias.

The British Pharmacopœia now includes a formulary section for the first time because revised monographs for many of the preparations that were formerly the subject of monographs in the British Pharmaceutical Codex have been added. In addition a section including surgical dressings, sutures and related materials has been introduced and certain other monographs that fall into well-defined classes have been removed from their customary positions in the main section of monographs and grouped together; this applies to blood preparations, to immunological products and to radiopharmaceutical materials. It has been found convenient to include the section of main monographs in a first volume of the Pharmacopœia and the formulary section, together with sections on specialised topics and the appendices, in a second volume.

European Pharmacopœia

The introduction to the British Pharmacopœia 1973 referred to the impact that the growing European Pharmacopœia was beginning to have on its requirements. This is now more apparent and the British Pharmacopœia Commission welcomes its collaboration with the authorities in other signatory states to the Convention and acknowledges the benefits that have accrued. It must, however, be recorded that the collaboration brings about its problems as well. For example if a demonstrable need arises to bring about rapid revision of a monograph in the British Pharmacopœia it is possible to put the revision into effect within a few months. Similar need for revision of a monograph included in the European Pharmacopœia requires the agreement of (at the time of writing) fourteen member states, followed by general acceptance of a date on which the changes are to be put simultaneously into effect in all countries. Understandably this can be a lengthy procedure.

The first edition of the European Pharmacopœia has now been completed and a second edition, which will include revised versions of the monographs in the first edition together with such new monographs as may from time to time be completed, is in the course of preparation. Many of the now inadequate monographs of the first edition have already been studied and revised versions have been accepted by the European Pharmacopœia Commission. Unfortunately they have not yet been published and no date for their entry into force has been announced. Where such agreed revised versions are available they have been included in edited form in an Annex to the section of main monographs in the British Pharmacopœia (or in the case of surgical materials as an Annex to the appropriate section), in part to give advance notice of future requirements but principally so that they may readily be invoked in replacement of the corresponding first edition monographs when dates for their simultaneous adoption throughout all member states have been decided. Thus, for example, two monographs for Nicotinamide are presented in Volume I of this Pharmacopœia. That in the main section of monographs (and distinguished by a five-pointed star) is the current monograph, being an edited version of that appearing in Volume II of the European Pharmacopœia. That included in the Annex is an edited version of the monograph that has already been adopted by the European Pharmacopœia Commission for inclusion in the second edition of the European Pharmacopœia.

During preparation of the European monographs for inclusion in this edition of the British Pharmacopœia certain errors have been detected in the original texts. Such errors have been brought to the attention of the European Pharmacopœia Commission for appropriate action but the British Pharmacopœia Commission has felt it necessary to maintain them uncorrected in this edition, pending their simultaneous correction in

all member states, in order to reproduce as faithfully as possible the European Pharmacopœia monographs.

Future publications

With the publication of this comprehensively revised edition of the Pharmacopœia the way has been opened for a more unified system of issuing published specifications and methods of evaluation for medicinal and related substances within the United Kingdom. It is the intention of the British Pharmacopœia Commission to issue Addenda to the Pharmacopœia at about twelve-monthly intervals. Apart from providing a means of issuing new and revised monographs with suitable frequency these Addenda will also be used to complete the presentation of monographs for materials formerly described in the British Pharmaceutical Codex 1973 and will facilitate the promulgation of monographs that may from time to time be added to the European Pharmacopœia. It is expected that successive addenda will be cumulative in nature so that at any given time users will simply need to have copies of the British Pharmacopœia 1980 and of the current Addendum available; the timing of publication of the fourteenth edition of the Pharmacopœia will then be determined, not by a somewhat artificial adherence to a rigidly fixed interval of years but by considerations of convenience dictated by the growing size of the cumulative addendum.

The basis of pharmacopœial requirements

With the issue of this new consolidated edition opportunity is being taken to stress once again the basis on which the requirements of the Pharmacopœia are established. The Pharmacopœia provides a publicly available statement concerning the quality of a product that is expected to be demonstrable at any time during its accepted shelf-life; it does not provide a collection of minimum standards with which a manufacturer must comply before release of a product. Change may occur during storage and distribution and the pharmacopœial requirements are set to acknowledge acceptable levels of change and to reject materials showing unacceptable levels. It follows that the prudent manufacturer will, where considerations of product stability demand, apply specifications that may be more exacting than those laid down in the Pharmacopœia. It also follows that a manufacturer may use any methods of analysis and any general control procedures that he deems appropriate to confirm to his own satisfaction that the product is acceptable. In doing so it must be recognised that, at any time during its acknowledged shelf-life, the product may be challenged independently by the methods of the Pharmacopœia and that compliance with the limits imposed will be required. In the event of doubt or dispute as to whether or not a material is of pharmacopœial quality, as a General Notice makes clear, the methods of the Pharmacopœia are alone authoritative.

This view of pharmacopœial requirements is also significant when considering the amount of sample to be taken for test. In an overall programme designed to give assurance of quality of a manufactured product the statistical validity of any sampling programme must be beyond doubt. The standards of the Pharmacopœia, on the other hand, are intended to apply to the sample available, perhaps the container of dispensed tablets provided to a patient in accordance with a prescription. The Pharmacopœia requires that twenty of those tablets should meet the test for Uniformity of Weight; a manufacturer establishing his sampling and testing protocol designed to ensure ultimate compliance with the pharmacopœial requirements will need to operate at a level designed to show with an acceptable degree of confidence that *any* twenty tablets, taken at random from a given batch, will meet the requirements.

Pharmacopœial methods and limits are thus set with the intention that they be used as compliance requirements and not as requirements

to guarantee total quality assurance. An article may be said to be of pharmacopœial quality if any sample of the size stipulated in the monograph meets the requirements at any time during storage, distribution and use of the material.

Arising from this it may be useful to underline that compliance of a product with pharmacopœial requirements demands that the product meets *all* aspects of the appropriate monograph and that those requirements be interpreted in the light of any relevant General Notices. In certain cases individual requirements of particular tests may seem to be incompatible with those of other tests; where this is the case such requirements have been framed intentionally. Take, for example, the requirements that might be applied to certain tablets. The overall content of active ingredient, as determined on a powdered sample of twenty tablets, might be 90.0 to 110.0 per cent of the prescribed or stated amount. Thus an assay result of 91.0 per cent would indicate compliance. For the Uniformity of content test a further ten tablets might be individually examined, each tablet being required to contain between 85 and 115 per cent of the mean value, with the possibility of a single exception between 80 and 120 per cent. Thus if nine out of ten tablets fall within the range (assuming the mean to be 91.0 per cent) 77.4 and 104.7 per cent and the tenth falls within the range 72.8 to 109.2 per cent then the tablets examined comply with that requirement. For the Dissolution test each tablet examined might be required to yield at least 70 per cent of the labelled claim into solution within forty-five minutes. It has been suggested that, since a single outrider tablet might contain as little as 72.8 per cent of the labelled claim and yet still fall within the acceptance limits for content, the requirements for dissolution should be relaxed to take this into account. In framing requirements, however, the view is taken that it is neither realistic nor profitable to attempt to compound the results of various tests in this way. Each test of a pharmacopœial monograph and the acceptance limit, is therefore framed as an individual entity with requirements based on values encountered in practice; compliance with the monograph requires compliance with each and every test.

Changes in style

Opportunity has been taken to introduce a number of changes in style throughout the Pharmacopœia. Most notable among these has been the replacement of normality by molarity as the means by which the concentrations of volumetric and certain other solutions are expressed. Furthermore, solutions whose strengths are required to be known with precision are indicated by the letters '*VS*'. Additionally the International System of Units (SI units) has been introduced wherever practicable. An approximate equivalent expressed in the more familiar c.g.s. system will be given in parentheses for an interim period that will extend for at least the currency of this edition. In continuance of a practice begun in the Addendum 1977 to the British Pharmacopœia 1973 the graphic formulæ, wherever possible, now indicate the stereochemical configuration of molecules and, an innovation in this edition, Chemical Abstracts Service Registry Numbers are also given in italic numerals at the head of appropriate monographs. The nomenclature used in the Appendices on Reagents has also been revised to accord with modern practices.

Attention is drawn to a change in policy regarding labelling requirements and the inclusion of cautionary statements. The labelling requirements in the Pharmacopœia are not exclusive and it should be clearly understood that at all times the laws and statutory provisions governing the statements to be declared on labels should be met, for example the provisions of labelling regulations issued pursuant to the Medicines Act 1968 and those of regulations relating to the labelling of hazardous materials. The Pharmacopœia may, however, require certain additional

information to be included, particularly where this is necessary to enable compliance with the provisions of a monograph to be determined.

As regards the inclusion of cautionary statements, for example, drawing attention to a hazardous property of a material, it has been decided that such statements should not be included in the Pharmacopœia unless warranted by exceptionally unusual circumstances. If statements were to be included in connection with certain materials the absence of statements in other cases might be taken as indicating that no hazards exist with such materials. In certain biological assays and tests in earlier editions of the Pharmacopœia attention has been drawn to the need to comply with the requirements of the Cruelty to Animals Act 1876; in other cases this injunction has not been included. Here too the British Pharmacopœia Commission has considered that such sporadic references to the Act might be misleading. All such specific references have therefore been omitted from this edition and the point has been covered by an extension of the General Notice on Biological Assays and Tests.

General Monographs

General monographs on specific types of dosage forms have always been regarded in earlier editions as being applicable only to the monographs of the Pharmacopœia. Many such general monographs are now included in the European Pharmacopœia and it has been agreed that the European requirements should be considered as applicable to all dosage forms of the type described, whether an individual monograph be included in the Pharmacopœia or not. Thus the general monograph on Tablets that is included in this edition consists of a preliminary part that is applicable to all tablets (this being an edited version of the requirements of the European Pharmacopœia) and a supplementary part that relates only to the specific monographs on individual tablets that are contained in the British Pharmacopœia. There is, for example, a test for Disintegration included in the European Pharmacopœia and this is invoked, with varying conditions of test, for all uncoated, coated, enteric-coated and effervescent tablets. Uncoated tablets, for example, are required to disintegrate within fifteen minutes *unless otherwise justified and authorised.* The italicised statement, which may find increasing use in such general situations, implies that an uncoated tablet should disintegrate within fifteen minutes unless a well-substantiated justification for some different time can be brought forward; such a justification should then be studied by an appropriate authority and authorised (for example, in a specific monograph of the Pharmacopœia or, if no monograph is included, with the agreement of a national licensing authority). In the case of certain monographs of the British Pharmacopœia where a dissolution test has been prescribed it has been considered justifiable to waive the disintegration test altogether. These considerations concerning general monographs do not apply to those for radiopharmaceuticals or for immunological products; both in the European and British Pharmacopœias these two general monographs relate only to the monographs included in the pharmacopœias and do not necessarily apply to preparations that are not the subject of monographs.

Dissolution Tests

Mention has been made above to the inclusion of dissolution tests in the Pharmacopœia. The British Pharmacopœia Commission has considered a list of all solid dosage forms in the Pharmacopœia 1973 and has established a preliminary selection for which the provision of a dissolution test at at early stage is thought to be necessary. These were selected as being materials that might give rise to clinical problems if the required dosage were not made available, or that have physical characteristics (for example, low solubility) that might give rise to problems, or that have been the subject of allegations of bio-inequivalence. For the majority of applications the British Pharmacopœia Commission will regard the test

as a measure of the proportion of drug capable of going into solution under standardised *in vitro* test conditions within a reasonable time. As such, the test is simply a physical requirement of the dosage form in question and it has not been considered essential to attempt to correlate results obtained with those obtained *in vivo*. For such applications of the test the criterion of acceptance is that a stated, substantial proportion of the total drug content of the preparation goes into solution under standardised conditions within a stated time period. For the majority of applications of the test already established the 'substantial proportion' is 70 per cent and the time is forty-five minutes. Such applications are referred to as falling into Category 1.

There are a few special cases (Category 2) where the test might be required to give further information. Such special applications might be necessary, for instance, where the active ingredient has a low therapeutic index or a short plasma half-life, where it may be selectively absorbed in a limited region of the gastro-intestinal tract or where it should not be released too rapidly. The need to achieve a specific and rapid action from a single dose might also merit inclusion of a material in this special category. In such cases the British Pharmacopœia Commission may wish to be satisfied that an adequate correlation with typical *in vivo* absorption characteristics has been demonstrated. Digoxin Tablets provide an excellent example of a Category 2 application of the test.

All preparations purporting to exhibit delayed or sustained-release characteristics are also being studied but certain of these materials are giving rise to particular problems. It is proving difficult, for example, to frame a satisfactory test for Slow Lithium Carbonate Tablets; the British Pharmacopœia 1973 contained a test based upon the use of the disintegration apparatus but this is acknowledged to be unsatisfactory. Nevertheless it has been decided to retain the old test pending development of a more satisfactory one rather than to make no statement whatever on the subject.

The apparatus and method of test to be used in all but the few cases where the solubility of the active ingredient is so low as to vitiate its application is described in Appendix XII D. The statement of the test procedure and the definition of the apparatus may be further improved as work aimed at identifying and overcoming causative factors of inter-laboratory variability continues.

In the present edition a dissolution test has been provided for the following preparations:

Chloroquine Phosphate Tablets
Chloroquine Sulphate Tablets
Chlorpropamide Tablets
Chlortetracycline Capsules
Digoxin Tablets
Isoniazid Tablets
Metformin Tablets
Oxytetracycline Capsules
Oxytetracycline Tablets
Phenoxymethylpenicillin Capsules
Phenoxymethylpenicillin Tablets
Phenylbutazone Tablets
Quinine Bisulphate Tablets
Quinine Sulphate Tablets
Tetracycline Capsules
Tetracycline Tablets
Tolbutamide Tablets
Warfarin Tablets

Infra-red Spectra: A companion volume

The concept of relying on published infra-red spectra as a basis for identification tests rather than requiring comparison of a spectrum prepared from a British Pharmacopœia Chemical Reference Substance with that of the material under examination was introduced in the British Pharmacopœia (Veterinary), published in 1977. Initial reports of the reliability of this procedure have resulted in a considerable extension of the policy in this edition. The collection of reference spectra for use with monographs is being published in a companion volume to the British Pharmacopœia. The advantages of adopting this changed policy are

principally that substantial economies both of time and expense will be effected by allowing a reduction in the number of Chemical Reference Substances that must be prepared, characterised, maintained and distributed and that the use of infra-red spectroscopy as a means of verifying identity can be extended to materials, for example certain Controlled Drugs, where the British Pharmacopœia Commission has been reluctant to establish reference substances for wide distribution.

Other innovations

In certain cases infra-red spectroscopy is not satisfactory as a means of identification and the use of nuclear magnetic resonance spectroscopy for this purpose has been introduced. Various corticosteroid sodium phosphates are now identified in this way and it is expected that use of the technique will be further extended as and where it is considered to be necessary. However, since it is recognised that nuclear magnetic resonance spectrometers are not generally available provision is made, in these and other instances, for a series of alternative tests to be carried out.

The use of high-pressure liquid chromatography (HPLC) introduced into the Pharmacopœia in 1977 has been extended in this edition and a general method for the technique has been added to the appendices. HPLC is proving particularly useful for certain formulations, for example Œstradiol Benzoate Injection, that can otherwise be analysed only by difficult and time-consuming methods.

A further innovation in this edition is the inclusion of a challenge test to evaluate the efficacy of antimicrobial preservatives in pharmaceutical products. It is stressed that the test is not a mandatory requirement to be applied to preparations of the Pharmacopœia; it is offered as a means by which the suitability of an intended preservative system for a product may be assessed during the development of that product. Thus the term 'suitable', when applied to an antimicrobial preservative agent, is now given a defined meaning. In connection with this test it should be noted that the criterion recommended for bacterial count in oral liquid preparations is intended to be made more stringent when further information on product performance is available; it is expected that a requirement that no organisms are recoverable after twenty-eight days and thereafter will be added some time during the currency of this edition.

In certain monographs of the Pharmacopœia a particular antimicrobial preservative agent or agents may have been specified. It has now been agreed that suitable alternative preservatives may be used, suitability in this instance implying that the proposed replacement is compatible with the preparation and that its efficacy is demonstrable when the challenge test is applied to the product. Whenever the term 'antimicrobial preservative' is used throughout the Pharmacopœia this is intended to cover protection against bacteria, moulds and yeasts.

The synonym Insulin that has long been used for Insulin Injection B.P. has been deleted in view of the introduction of a monograph on a purified crystalline single-peak insulin substantially free from proinsulin and having a potency of not less than 26 Units per mg on the anhydrous basis. It is stressed that the various preparations of insulin described in monographs at the present time are the traditional preparations prepared from crystalline insulin having a potency, on the anhydrous basis, of not less than 23 Units per mg. Thus, contrary to the standard practice that applies elsewhere throughout the Pharmacopœia, the insulin preparations, Insulin Injection for example, do not necessarily have to be prepared from Insulin B.P. Work is proceeding to develop a series of monographs based on the purified proinsulin-free material; these will bear appropriately distinctive titles.

Another change in this edition that has had far-reaching effects is that the monograph formerly entitled Alcohol (95 per cent) has now been

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