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Notice

Patents

In this Pharmacopoeia 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 Pharmacopoeia neither conveys, nor implies, licence to manufacture.

Preface

The British Pharmacopoeia 1993 is published for the Health Ministers on the recommendation of the Medicines Commission in accordance with section 99(6) of the Medicines Act 1968.

The Medicines Commission believes that the role of the Pharmacopoeia 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 Pharmacopoeia 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 Pharmacopoeia in this connection is clear.

The Medicines Commission wishes to record appreciation for the services of all who have contributed to this important work.

British Pharmacopoeia Commission

The British Pharmacopoeia Commission is appointed by the Secretary of State concerned with health in England, the Secretaries of State respectively concerned with health and with agriculture in Wales and in Scotland, the Minister of Agriculture, Fisheries and Food, the Department of Health and Social Services for Northern Ireland and the Department of Agriculture for Northern Ireland, acting jointly, in exercise of their powers under section 4 of the Medicines Act 1968.

The duties of the British Pharmacopoeia Commission are as follows:

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

(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 Pharmacopoeia published in 1968 or any new edition of it;

(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 Pharmacopoeia) of any list of names and the preparation under that section as given effect by section 102(3) of the Act of any amendments of any published list;

(d) the preparation under section 99(3)(b) of the Act of any compendium or any new edition thereof;

(e) the preparation under section 99(3)(b) of the Act, as given effect by section 102(1) thereof, of any amendments to any such compendium.

Members of the British Pharmacopoeia Commission are appointed by Ministers, having regard to recommendations made by the Medicines Commission. Appointments are usually for a (renewable) term of 4 years.

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[1]Term of office ended 31 December 1991.
[2]Term of office ends 31 December 1993.
[3]Term of office ends 31 December 1995.
[4]Resigned September 1992.
[5]From 1 November 1991.
[6]Retired 31 October 1991

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*Deceased December 1992

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The membership of the European Pharmacopoeia Commission on 1 December 1992 was as follows:

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The membership of the Groups of Experts on 1 December 1992 was as follows:

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Introduction

This, the fifteenth, edition of the British Pharmacopoeia, has been prepared by the British Pharmacopoeia Commission with the collaboration and support of its advisory committees and other experts. In addition to these individuals directly involved in preparation of the Pharmacopoeia, the British Pharmacopoeia Commission would like to thank all those users of the Pharmacopoeia from the United Kingdom and overseas who have provided comment on pharmacopoeial issues. Dialogue with users is an essential element of pharmacopoeial development and the British Pharmacopoeia Commission welcomes constructive comment from whatever quarter.

The New Edition

This new edition of the Pharmacopoeia contains 2040 monographs for substances and articles used in the practice of medicine. The effective date for this edition is 1 December 1993. From this date this edition supersedes the British Pharmacopoeia 1988 as amended by its various addenda. If a monograph that appeared in the earlier edition has not been included in this edition then that monograph remains effective, in accordance with Section 65(4) of the Medicines Act 1968.

Volume I contains the monographs for medicinal and auxiliary substances, and the infrared spectra, whilst Volume II comprises the sections dealing with formulated preparations, blood products, immunological products, radiopharmaceutical preparations and surgical materials together with the appendices and a comprehensive index. The General Notices are printed on tinted paper in each volume.

The opportunity provided by publication of the new edition has been used to consolidate the main volumes of the previous edition with its four addenda, to review editorial policy and to introduce a number of changes of style throughout the Pharmacopoeia. Attention is drawn to the more significant changes elsewhere within the relevant sections of the Introduction.

Major changes have been made to the order in which monographs are presented in the section on Formulated Preparations and to the contents of the section on Surgical Materials. Another obvious change is the introduction at the beginning of each monograph of the side-heading Definition followed in some cases by the side-heading Production. This editorial change has been made to clarify the status of the opening paragraphs of monographs and to provide a consistent style throughout the Pharmacopoeia.

An editorial style closer to that of the European Pharmacopoeia has been adopted where it is considered helpful to the user of the British Pharmacopoeia. For example, the status of solubility statements has been clarified by their inclusion under the side-heading Characteristics and by extensive use of the European Pharmacopoeia terms for expressing approximate solubility as given in the revised General Notice. Similarly the European Pharmacopoeia names for many reagents have been introduced either in place of or in addition to the name previously employed in the British Pharmacopoeia. Not all the changes towards the style of the European Pharmacopoeia have been

introduced throughout this new edition. They will be introduced progressively as monographs are added or replaced in subsequent addenda.

Some Additions

Monographs included in the Pharmacopoeia for the first time are listed at the end of this Introduction. These include the diuretic bumetanide, the antipsychotic thioridazine, injections of the antibiotics amoxycillin and clindamycin and enteric-coated tablets of the anticonvulsant sodium valproate.

Also included are new European Pharmacopoeia monographs for the histamine H_2-receptor antagonist cimetidine, the artificial sweetener sodium cyclamate and for a variety of amino acids. A new European Pharmacopoeia general monograph for products of recombinant DNA technology, the requirements of which are currently invoked in the new monograph for human insulin, will find increasing application as other genetically engineered materials are introduced into the Pharmacopoeia. The introduction to the European Pharmacopoeia of monographs for the hormones oxytocin and corticotrophin has led to the suppression of the European Pharmacopoeia monographs for the associated dosage forms from 1 January 1993. However an amended monograph for oxytocin injection is retained in Volume II of this edition.

European Pharmacopoeia

Approximately 800 monographs now comprise Part II of the second edition of the European Pharmacopoeia and have been published by means of sixteen loose-leaf fascicules. In accordance with established practice, all these monographs, with the exception of the small number listed at the end of the Introduction, are reproduced in an edited form either in this edition of the British Pharmacopoeia or, where appropriate, in the associated edition of the British Pharmacopoeia (Veterinary). The user of the British Pharmacopoeia thus benefits by finding within this one, comprehensively indexed, compendium all current pharmacopoeial standards for medicines for human use in the United Kingdom.

Edited versions of European Pharmacopoeia monographs are distinguished by a five-pointed star against the title. It is emphasised that in the event of doubt of interpretation of such texts the European Pharmacopoeia text published in English under the direction of the Council of Europe must be consulted. A General Notice stresses the mandatory nature of this injunction.

The majority of edited European Pharmacopoeia monographs are to be found in Volume I of the British Pharmacopoeia (medicinal and pharmaceutical substances) and in those sections of Volume II devoted to blood products, immunological products and radiopharmaceutical preparations. The current policy of the European Pharmacopoeia Commission is to concentrate effort on the preparation of monographs within these categories and on general monographs for dosage forms. The latter are of special importance because their provisions apply to all formulated preparations of the type defined whether or not a specific formulated preparation is itself the subject of a pharmacopoeial monograph. Thus, for example, the provisions of the European Pharmacopoeia general monograph for Tablets apply to any preparation referred to as a tablet and not only to those tablets such as Aspirin Tablets or Enteric-coated Sodium Valproate Tablets that are included in the British Pharmacopoeia. Similarly the European Pharmacopoeia general monograph for Topical Semi-solid Preparations applies to *all* medicinal creams, gels, ointments and pastes. Recognition of the trend within the European Pharmacopoeia towards general monographs of very broad

scope such as that for Preparations for Inhalation and that for Nasal Preparations has led to a restructuring of the section of the British Pharmacopoeia on Formulated Preparations. This is described in more detail below.

A new European Pharmacopoeia general monograph of a rather different kind is that for products of recombinant DNA technology. The provisions of this monograph, included in Volume I of the British Pharmacopoeia, are intended to apply in future not only to biological substances such as human insulin but also to preparations such as vaccines. These provisions relate to features of the development, validation and control of the manufacturing processes associated with the use of genetically engineered cells. These production requirements are intended to complement and underpin the specific test requirements included in individual monographs.

Another new European Pharmacopoeia text of special note is the test for efficacy of antimicrobial preservation included in Appendix XVI C. The test methodology is essentially similar to that previously included in the British Pharmacopoeia. As with the previous BP appendix, the test has been accorded non-mandatory status in the Pharmacopoeia. It is intended to serve as a model offering a manufacturer guidance concerning this aspect of quality and a foundation on which he can build to meet his own particular needs. The testing procedure is intended to serve as a means whereby, during product development, a manufacturer can assess the efficacy of any antimicrobial preservative included in the product. If during development a fully quantitative, comparative evaluation of different preservative systems would be useful, the procedure described in the appendix could be extended to incorporate an estimation of initial microbial death rates.

The present European Pharmacopoeia text provides criteria for parenteral, ophthalmic and oral preparations only. However the British Pharmacopoeia continues to provide criteria for the full range of products covered in the previous edition. Additional statements for topical preparations and ear preparations are therefore included in Appendix XVI C. The criteria for topical preparations are those previously included in the British Pharmacopoeia. The criteria for ear preparations are equivalent to the A criteria now specified for ophthalmic preparations thus maintaining parity between these two types of product.

A novel feature of the European Pharmacopoeia text is the inclusion of two sets of criteria (A and B) for parenteral and ophthalmic preparations. The A criteria express the recommended efficacy to be achieved, that is, they represent generally applicable 'target' criteria. It is recognised that for a number of products these target criteria are unlikely to be achieved except at the expense of some other property of equal or greater importance. The alternative criteria to be met in these circumstances are a matter for agreement between the manufacturer and the licensing authority and should take account of any special considerations relevant to the specific product. The B criteria for parenteral and ophthalmic products were adopted by the European Pharmacopoeia Commission in deference to those member states that wanted published guidance on the minimum values below which any alternative criteria should not fall.

The Basis of Pharmacopoeial Requirements

A proper understanding of the basis on which the requirements of the Pharmacopoeia are established is essential to the correct interpretation of the requirements.

The Pharmacopoeia contributes significantly to the overall control of the quality of medicinal products and provides a publicly available

statement concerning the quality that a product or a component of a product is expected to meet at any time during its period of use. Pharmacopoeial specifications are used within licensing systems and by manufacturers, suppliers, purchasers and those acting on behalf of consumers of medicinal products.

A manufacturer must recognise that a product or material may be challenged at any time during its claimed period of use by the methods of the Pharmacopoeia and that it must then comply with the pharmacopoeial requirements. These requirements allow for acceptable levels of change that may occur during storage and distribution and reject articles showing unacceptable levels of change. Frequently a manufacturer will need to apply more stringent test limits at the time of release of a batch of the product or material in order to ensure compliance. As stated in the General Notices, a manufacturer may assure himself that the requirements of the Pharmacopoeia will be met by means other than routinely performing all of the tests prescribed in the Pharmacopoeia. It is emphasised that the circumstances under which, and the frequency with which, tests of the Pharmacopoeia should be performed by a manufacturer as part of his overall quality assurance are ultimately matters for agreement between the manufacturer and the appropriate licensing authority.

The requirements included in a monograph, other than any instructions given under the side-heading Production (see below), are designed to provide the means by which an independent judgement can be made as to the overall quality of a particular article. A manufacturer in possession of detailed knowledge of the manufacturing process may have no need to carry out certain tests. The example of some impurity tests in monographs for formulated preparations is discussed in more detail below. The methods described in the Pharmacopoeia must be robust because they are intended to be used by analysts in a wide range of laboratories, sometimes on an infrequent basis. Understandably, a manufacturer may wish to use other methods that may be more suitable for frequent use or automation and is entitled to do so. However in the event of any doubt or dispute as to whether or not a material is of pharmacopoeial quality, as the General Notice on Assays and Tests makes clear, the methods of the Pharmacopoeia alone are authoritative.

This view of pharmacopoeial requirements is also significant when considering the size 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 Pharmacopoeia, 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 Pharmacopoeia requires that twenty of those tablets should meet the test for Uniformity of weight. A manufacturer establishing a sampling and testing protocol designed to ensure ultimate compliance with the pharmacopoeial 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.

Pharmacopoeial methods and limits are set with the intention that they should be used as compliance requirements and not as requirements to guarantee total quality assurance. An article is not of pharmacopoeial quality if any sample of the size stipulated in the monograph taken at any time during storage, distribution and use within the accepted shelf-life fails to meet all of the requirements.

Arising from this it may be useful to underline that compliance of a product with pharmacopoeial requirements demands that the product