British Pharmacopoeia 2008

Volume I

Introduction
General Notices
Monographs
Medicinal and Pharmaceutical Substances (A–I)

Incorporating the requirements of the 5th edition of the European Pharmacopoeia 2004 as amended by Supplements 5.1 to 5.8

British Pharmacopoeia 2008

Volume I

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The monographs of the Fifth Edition of the European Pharmacopoeia (2004), as amended by Supplements 5.1 to 5.8 published by the Council of Europe are reproduced either in this edition of the British Pharmacopoeia or in the associated edition of the British Pharmacopoeia (Veterinary).

See General Notices

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British Pharmacopoeia 2008

Volume I

FOREWORD

Since 1864, the British Pharmacopoeia has been providing authoritative official standards for pharmaceutical substances and medicinal products. The 2008 edition (BP 2008) continues this tradition. It makes an important contribution, therefore, to the role of the Medicines and Healthcare products Regulatory Agency in protecting public health by setting publicly available standards for the quality of medicines.

In addition to expanding the numbers of monographs for licensed formulated products, this edition supports the new regulatory work in the fields of herbal and complementary medicines by providing new monographs for traditional herbal medicinal products and for homoeopathic stocks and mother tinctures. The 2008 edition has also begun to improve the control of the quality of unlicensed medicines by providing standards for extensively used unlicensed formulations together with further legal and ethical guidance on the preparation and supply of these products.

As a testament to the quality of their work in preparing and publishing the BP 2008, the processes and activities of the British Pharmacopoeia Secretariat were brought this year within the scope of the Medicines and Healthcare products Regulatory Agency's registration to the quality management system standard ISO 9001:2000.

The British Pharmacopoeia maintains close ties with the work of the European Pharmacopoeia and continues to play a significant role in the standard-setting process in Europe, participating in the activities of the European Directorate for the Quality of Medicines and Healthcare, and influencing the decisions of the European Pharmacopoeia Commission through the United Kingdom Delegation. The texts and monographs of the European Pharmacopoeia form an integral part of the BP 2008.

Annually updated, the British Pharmacopoeia is the only comprehensive collection of standards for UK medicinal substances. It is essential for all individuals and organisations involved in pharmaceutical research, development, manufacture, quality control and analysis.

Sir Alasdair Breckenridge
Chairman, MHRA

Notices

Monographs of the European Pharmacopoeia are distinguished by a chaplet of stars against the title. The term European Pharmacopoeia, used without qualification, means the fifth edition of the European Pharmacopoeia comprising, unless otherwise stated, the main volume, published in 2004 as amended by any subsequent supplements and revisions.

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.

Effective dates New and revised monographs of national origin enter into force on 1 January 2008. Monographs of the European Pharmacopoeia have previously been published by the Council of Europe and have been brought into effect by means of Notices published in the Belfast, Edinburgh and London Gazettes.

Preface

The British Pharmacopoeia 2008 is published for the Health Ministers on the recommendation of the Commission on Human Medicines in accordance with section 99(6) of the Medicines Act 1968.

The Commission on Human Medicines believes that the British Pharmacopoeia contributes significantly to the overall control of the quality of medicinal products by providing an authoritative statement of the quality that a product, material or article is expected to meet at any time during its period of use. The Pharmacopoeial standards, which are publicly available and legally enforceable, are designed to complement and assist the licensing and inspection processes and are part of the system for safeguarding purchasers and users of medicinal products.

The Commission on Human Medicines wishes to record its appreciation of the services of all those who have contributed to this important work.

British Pharmacopoeia Commission

The British Pharmacopoeia Commission is appointed by the NHS Appointments Commission, the body responsible for appointments to all of the Medicines Act 1968 Advisory Bodies.

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(6) of the Act, of any compendium, or any new edition thereof, containing information relating to substances and articles which are or may be used in the practice of veterinary medicine or veterinary surgery;

(e) to frame clear and unequivocal technical advice in order to discharge the Commission's responsibilities both for the British Pharmacopoeia, the British Pharmacopoeia (Veterinary) and British Approved Names and as the national pharmacopoeial authority with respect to the European Pharmacopoeia.

Members of the British Pharmacopoeia Commission are appointed for a (renewable) term of 4 years and, under the requirements laid down by the Office of the Commissioner for Public Appointments, can serve for a maximum of 10 years.

Membership of the British Pharmacopoeia Commission

The list below includes those members who served during the period 2006 to 2007.

Chairman Professor David Woolfson BSc PhD CChem FRSC MPSNI
Professor of Pharmaceutics, Queens University of Belfast

Vice-Chairman Mr V'Iain Fenton-May BPharm MI PharmM FRPharmS
Specialist Quality Controller to the Welsh Hospitals

Dr Anthony H Andrews BVetMed PhD MBIAC DipECBHM FRSM MRCVS
Veterinary Consultant

Professor Graham Buckton BPharm PhD DSc AKC FRPharmS CChem FRSC
Professor of Pharmaceutics; School of Pharmacy, University of London

Professor Donald Cairns BSc PhD MRPharmS CSci CChem MRSC
Associate Head, School of Pharmacy, Robert Gordon University, Aberdeen

Mr Barry Capon CBE (*Lay representative*)
Non-executive Director, Norfolk and Waveney Mental Health Partnership

Professor Alastair Davidson BSc PhD FRPharmS CChem FRSC
Visiting Professor of Pharmaceutical Sciences, University of Strathclyde

Mrs Margaret A Dow MSc PhC
Consultant in the regulation of biological and biotechnological products

Dr Thomas D Duffy BSc PhD FRPharmS CChem MRSC FIQA MRQA
Consultant in quality management systems, quality assurance and training in production, development and QC Laboratories

Mr Christopher Goddard BSc DIS CSci EurChem CChem FRSC
Quality Control Manager, Ashton Pharmaceuticals Limited

Dr Rodney L Horder BPharm PhD MRPharmS
Vice President, Global Pharmaceutical R & D Quality Assurance, Abbott Laboratories

Dr Aileen M T Lee BVMS PhD MRCVS
Member of the Veterinary Medicines Directorate
Specialism: Regulation of Veterinary Immunological Products

Professor Anthony C Moffat BPharm PhD DSc CChem FRSC FRPharmS FFIP
Head, Centre for Pharmaceutical Analysis, The School of Pharmacy, University of London

	Dr Lincoln Tsang BPharm LLB PhD FRSC FIBiol FRSA MRPharmS Solicitor *Life Sciences Lawyer; Partner, Arnold & Porter LLP*
	Mrs Josephine Turnbull LLB (*Lay representative*) *Chairman of County Durham and Darlington Priority Services Trust; member of the Parole Board of England and Wales*
	Professor Elizabeth Williamson BPharm PhD MRPharmS *Professor of Pharmacy, University of Reading*
	Professor Peter York BSc PhD DSc FRPharmS CChem FRSC *Professor of Physical Pharmaceutics, University of Bradford*
Secretary and Scientific Director	Dr Gerard Lee BPharm PhD FRPharmS MRSC CChem

Membership of Expert Advisory Groups, Panels of Experts and Working Parties

The Commission appointed the following Expert Advisory Groups, Panels of Experts and Working Parties to advise it in carrying out its duties. Membership has changed from time to time; the lists below include all who have served during the period 2006 to 2007.

EXPERT ADVISORY GROUPS

ABS: Antibiotics (formerly Committee E)

R L Horder (*Chairman*), P York (*Vice-Chairman*), A Ambrose, A H Andrews, J F Chissell, J Dolman, P Ellis, S Green, R Harryman, A Livingstone, W Mann, W F H McLean, S Patel, C G Taylor, I R Williams

CX: Excipients (disbanded, 30 June 2006)

G Buckton (*Chairman*), C Mroz (*Vice-Chairman*), E Anno, A C Cartwright, R Cawthorne, M Kearsley, B R Matthews, M I Robertson

HCM: Herbal and Complementary Medicines (formerly Committee G)

A C Moffat (*Chairman*), L A Anderson (*Vice-Chairman*), M Berry, K Chan, T Chapman, A Charvill, K Helliwell, P J Houghton, C Leon, W F H McLean, J D Phillipson, M Pires, J Sumal, E Williamson (*Corresponding member* B P Jackson)

MC1: Medicinal Chemicals (formerly Committee A)

A G Davidson (*Chairman*), D Cairns (*Vice-Chairman*), M Ahmed, L Anderson, J C Berridge, M Broughton, A J Caws, P Fleming, A Hardy, W J Lough, D Malpas

MC2: Medicinal Chemicals (formerly Committee B)

T D Duffy (*Chairman*), C T Goddard (*Vice-Chairman*), D Billington, F Breslin, M Cole, B M Everett, K Goode, A J Hutt, S Jones, M A Lee, J Lim, K McKiernan, B Midcalf, P Murray, M Turgoose

MC3: Medicinal Chemicals (formerly Committee D)

V Fenton-May (*Chairman*), E Williamson (*Vice-Chairman*), S Arkle, J F Chissell, C T Goddard, W J Poling, W K L Pugh, G G Skellern, W H Smith, R Tomlinson, R Torano, I R Williams

NOM: Nomenclature (formerly Panel N)

J K Aronson (*Chairman*), L Tsang (*Vice-Chairman*), M Ahmed, D Cousins, G Gallagher, P W Golightly, D Masieh, A McNaught, H McNulty, G P Moss, R J Taylor, R Thorpe (*Corresponding members* R G Balocco Mattavelli, E M Cortés Montejano, J Robertson)

PCY: Pharmacy (formerly Committee P) R L Horder (*Chairman*), A D Woolfson (*Vice-Chairman*), M Aulton, E Baker, S Branch, G Buckton, G Davison, G Eccleston, D Elder, R Lowe, B R Matthews, J F McGuire, S C Nichols, R Shaw, M P Summers, K Truman, P Wood

PANELS OF EXPERTS

BIO: Biological and Biotechnological Products (formerly Panel H) M A Dow (*Chairman*), L Tsang (*Vice-Chairman*), C Booth, A F Bristow, D H Calam, J Cook, T Forsey, R Johnson, J Lawrence, B Mason, A Onadipe, A M Pickett, S Poole, N Randall, D Sesardic, P Sheppard, W J Tarbit, J N A Tettey, A H Thomas, R Thorpe, S Vass

BLP: Blood Products (formerly Panel HB) B Cuthbertson, A R Hubbard, J Lawrence, T J Snape, R Thorpe, P Varley

IGC: Inorganic and General Chemicals (formerly Panel CI) C T Goddard (*Chairman*), A C Cartwright, B M Everett, P Henrys, D Malpas, C Mroz, I D Newton

J: Immunological Products (disbanded, 30 June 2006) M J Corbel, M A Dow, A M Pickett, D Sesardic, A H Thomas

MIC: Microbiology (formerly Panel M) V Fenton-May (*Chairman*), A H Andrews, R Baird, C Booth, S Denyer, S Gorman, D P Hargreaves, R Johnson, B R Matthews, W F H McLean, P Newby, P Taylor

RAD: Radioactive Materials (formerly Panel R) S R Hesslewood, D Lui, A M Millar, R D Pickett, S Waters

VIP: Veterinary Immunological Products (formerly Panel JV) A M T Lee (*Chairman*), A H Andrews, K Redhead, J Salt, P W Wells

WORKING PARTIES

CX: Excipients G Buckton (*Chairman*), C Mroz (*Vice-Chairman*), E Anno, R Cawthorne, B R Matthews, M I Robertson

UM: Unlicensed Medicines V Fenton-May (*Chairman*), T D Duffy (*Vice-Chairman*), I Beaumont, C Cable, P Forsey, S Jones, A Lowey, A Nunn, A Pandya, J Smith, D Wallace

Current members of staff of the British Pharmacopoeia Laboratory who have taken part in the production of this edition include:

R Gaur (*Laboratory Manager*), M Azizi, L Fletcher, A Jordan, R Mannan, A Panchal, D Parmar, K Patel, M Patel, N Patel, J Rana, S Rihal

British Pharmacopoeia Staff

Members of staff who have taken part in the production of this edition include:

Secretariat M Vallender (*Editor-in-Chief*)

S Young (*Head of Science*)

A Bentley, M Barrett, A Evans, P Holland, M O'Kane, R A Pask-Hughes, F J Swanson, N Thomas, R L Turner

Administrative M Cumberbatch, B F Delahunty, W Jeffries, L Phillips

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Introduction

The British Pharmacopoeia 2008 supersedes the British Pharmacopoeia 2007. It has been prepared by the British Pharmacopoeia Commission, with the collaboration and support of its Expert Advisory Groups and Panels of Experts, and contains approximately 3100 monographs for substances, preparations and articles used in the practice of medicine. Some of these monographs are of national origin while others have been reproduced from the 5th edition of the European Pharmacopoeia. This edition, together with its companion edition, the British Pharmacopoeia (Veterinary) 2008, incorporates all the monographs of the 5th edition of the European Pharmacopoeia as amended by Supplements 5.1 to 5.8. The user of the British Pharmacopoeia thereby benefits by finding within this one, comprehensively indexed, compendium all current United Kingdom pharmacopoeial standards for medicines for human use. The new edition comprises six volumes as follows.

Volumes I and II	Medicinal Substances
Volume III	Formulated Preparations, Blood-related Products, Immunological Products, Radiopharmaceutical Preparations, Surgical Materials and Homoeopathic Preparations
Volume IV	Infrared Reference Spectra, Appendices, Supplementary Chapters and Index
Volume V	British Pharmacopoeia (Veterinary) 2008
Volume VI	CD-ROM version of the BP 2008 and BP (Vet) 2008

Effective Date

The effective date for this edition is 1 January 2008.

Where a monograph which appeared previously in an earlier edition of the British Pharmacopoeia has not been included in this edition, it remains effective in accordance with Section 65(4) of the Medicines Act 1968.

Expert Advisory Groups and Panels of Experts

A comprehensive review of the membership of the Committees and Panels of Experts was undertaken. The Committees were renamed Expert Advisory Groups (EAGs) and the letter designations for the EAGs and Panels of Experts were changed to reflect more closely the name of the EAG and Panel. The Committee on Excipients was disbanded and its work will now be undertaken by Working Parties of the Pharmacy EAG. The Panel of Experts on Immunological Products was disbanded and the remit of the panel incorporated into that of the Panel of Experts on Biological and Biotechnological Products. The Panel of Experts on Nomenclature was replaced by a new Expert Advisory Group on Nomenclature.

General Notices

Four areas of change have been introduced to the British Pharmacopoeia General Notices (Part II) as follows.

Definition of terms

A new General Notice has been added to clarify terms such as 'about', 'corresponds' and 'similar' used throughout the publication.
The clarification is intended to facilitate the interpretation of monographs of the British Pharmacopoeia.

Crude Drugs; Traditional Herbal and Complementary Medicines; Homoeopathic Medicines

The General Notice on Crude Drugs has been broadened to encompass traditional herbal and complementary medicines. A separate General Notice has also been added to cover Homoeopathic Medicines.

Storage

This General Notice has been amended to clarify the use of the terms 'tamper-evident containers' and 'tamper-proof containers' throughout the Pharmacopoeia.

Unlicensed Medicines

As part of the quality control of Unlicensed Medicines, a General Notice that applies to Unlicensed Medicines has been introduced in this new edition.

Additions

A list of monographs included for the first time in the British Pharmacopoeia 2008 is given at the end of this introduction. It includes 49 new monographs of national origin and 60 new monographs reproduced from Supplements 5.6, 5.7 and 5.8 of the European Pharmacopoeia.

Traditional Herbal Medicines

Work has continued on the development of monographs for herbal materials and processed herbs used in Traditional Chinese Medicines. This new edition sees the publication of 7 new monographs. It is emphasized that, although requirements for the *quality* of the material are provided in the monograph to assist the registration scheme by the UK Licensing Authority, the British Pharmacopoeia Commission has not assessed the safety of the material in traditional use.

Homoeopathic Preparations

A new initiative to support the simplified registration scheme by the UK Licensing Authority has been introduced with the publication of 5 new monographs for homoeopathic stocks and mother tinctures.

Omeprazole Preparations

Attention is drawn to the new monographs for Gastro-resistant Omeprazole Capsules and Gastro-resistant Omeprazole Tablets published in this edition. It is important for these proton-pump inhibitors, used for the short-term treatment of duodenal ulcers and acid reflux, to release the active moiety at pH values above 4.5 to avoid degradation of the active ingredient and potential inefficacy. The two monographs for Gastro-resistant Omeprazole

formulated preparations therefore include performance–related requirements to check the integrity of their coating at pH 4.5 to ensure that the active moiety is not released prematurely.

Unlicensed Medicines

With this new edition, requirements in a general monograph have been introduced to apply to all Unlicensed Medicines. 9 individual monographs for unlicensed formulations have also been included. These individual monographs are characterised by a statement that they are unlicensed in the United Kingdom. The general and individual monographs are intended to apply to all types of Unlicensed Medicines, that is, those formulations manufactured under a specials licence and those prepared extemporaneously under the supervision of a pharmacist.

Revisions

National monographs which have been amended technically by means of this edition are also listed at the end of this introduction. For the benefit of the reader this list indicates the section, or sections, of each monograph which has/have been revised.

The list is as comprehensive as practicable. However, to ensure that the reader uses the current standard, it is essential to refer to the full text of each individual monograph.

Infrared Reference Spectra

As with the previous edition, the reference spectra are placed in alphabetical order within this edition. Six new spectra have been added to the collection.

Appendices

In order to clarify and facilitate interpretation of British Pharmacopoeia monographs, statements on injection volume have been added to Appendix III B (Gas Chromatography) and Appendix III D (Liquid Chromatography).

A review and reorganisation of Appendix XII has been carried out for this edition. Appendix XII A covers methods of test relating to Disintegration; Appendix XII B covers methods of test relating to Dissolution and Appendix XII C covers methods of test relating to Consistency of Formulated Preparations. The Disintegration Test for Enteric-coated tablets has been deleted since it is covered in the European Pharmacopoeia general monograph for Tablets. A table correlating the new and former Appendices is published following the section on Contents of the Appendices in Volume IV of this edition.

Appendix XII A2 (Disintegration Test for Suppositories and Pessaries) has been amended to distinguish between requirements of the European Pharmacopoeia and additional requirements that apply to monographs of the British Pharmacopoeia.

Revisions have been made to Appendix XXIII. The title has been amended to Weights and Measures and is sub-divided into two sequential sections, the first, Appendix XXIII A, being the International System of Units which has been revised and the second, Appendix XXIII B, being a new BP Appendix on Conversion Tables for Commonly Used Units. This Appendix complements the introduction of a new Supplementary Chapter relating to Pharmacopoeial Calculations.

Supplementary Chapters

Dissolution Testing of Solid Oral Dosage Forms

A review of the Supplementary Chapter on Dissolution Testing of Solid Oral Dosage Forms (Supplementary Chapter I E) was undertaken for consistency with internationally harmonised guidance notes. The guidance on dissolution testing included in Ph Eur method 2.9.3 Dissolution Test for Solid Dosage Forms is included as an Annex in the revised Chapter.

Monograph Development: Mechanism

The British Pharmacopoeia policy on Monograph Initiation is included for the first time in this Supplementary Chapter (III B) and the schematic diagram for monograph development has been simplified.

Validation of Analytical Procedures

This Supplementary Chapter (III F) has been revised and the definitions of the terms have been harmonised with ICH guidelines. A summary table showing validation requirements for different procedures has been added to this Chapter.

Unlicensed Medicines

This Supplementary Chapter (V) has been revised. Guidance on the legal requirements has been expanded to clarify the regulations for imported unlicensed medicines. Labelling requirements for unlicensed medicines are now part of the new General Monograph on Unlicensed Medicines. A new section on Standards for Preparation and Manufacture of Unlicensed Medicines has been added which also explains the differences between extemporaneous preparation and batch manufacture.

Chromatograms for Information

Further chromatograms for information that are not published in the European Pharmacopoeia but are available on the European Pharmacopoeia Internet site (www.pheur.org) have been added to British Pharmacopoeia Supplementary Chapter IV I.

Pharmacopoeial Quantitative Analysis

In response to frequent requests from users of the British Pharmacopoeia, a new Supplementary Chapter, VI, entitled Pharmacopoeial Quantitative Analysis has been introduced in this edition. The Chapter is sub-divided into sections, the first, Supplementary Chapter VI A, being Pharmacopoeial Calculations, the second, VI B, being Titrimetric Analysis and the third, VI C, the provision of Indicator Colour Changes. These Supplementary Chapters are intended as a useful guide to the analyst and to complement existing Appendices and general methods. Examples of colour change intervals for common indicators are included in Supplementary Chapter VI C and, for the first time, the change interval charts are printed in colour.

Editorial Changes

Action and use

An extensive review of the Action and use statements has been undertaken. Changes have been made to the monographs included in Volumes I and II. A combined statement is included indicating, where known, the pharmacological action and the therapeutic use of the substance or