Fourth Edition, *First Supplement*

The First Supplement, published in 2008, contained new and revised monographs for pharmaceutical substances and dosage forms together with additions and amendments to the texts published in Volumes 1 and 2. As with the main volumes, the First Supplement was published simultaneously in print, as a CD-ROM and online. The replacement CD-ROM contained the complete text of the Fourth Edition comprising Volumes 1 and 2 as amended and augmented by the text of the First Supplement.

The new monographs published in the First Supplement incorporated additional antiretroviral substances, antiretroviral dosage forms and antituberculosis dosage forms, including 2-, 3-, and 4-component fixed-dose preparations.

The related decisions and final recommendations by this Expert Committee can be retrieved in the WHO Technical Report Series, Nos 929, 937 and 943. The specific section can be provided upon request or alternatively consulted on the web: http://www.who.int/medicines/services/expertcommittees/pharmprep/en/index.html

New monographs. New monographs are included for five antiretroviral substances, for 16 antiretroviral dosage forms, incorporating two fixed-dose combination preparations, for one antimalarial dosage form and for six antituberculosis dosage forms, including 2-, 3-, and 4-component fixed-dose preparations. Such specifications support the joint UNICEF-WHO-UN Prequalification Team. In developing these monographs WHO has worked closely with manufacturers, national authorities and national quality control laboratories. Details are as follows:

NEW MONOGRAPHS

Pharmaceutical substances

- -Abacavir sulfate
- -Efavirenz
- -Lamivudine
- -Stavudine
- -Zidovudine

Dosage forms

General monographs

- -Liquid preparations for oral use
- -Oral powders

Specific monographs

- -Abacavir oral solution
- -Abacavir sulfate tablets
- -Didanosine oral powder
- -Didanosine liquid for oral use, paediatric
- -Didanosine tablets
- -Doxycycline capsules
- -Isoniazid and ethambutol hydrochloride tablets
- -Lamivudine oral solution
- -Lamivudine tablets
- -Nelfinavir mesilate oral powder
- -Nelfinavir mesilate tablets
- -Rifampicin capsules
- -Rifampicin tablets
- -Rifampicin and isoniazid tablets
- -Rifampicin, isoniazid and pyrizinamide tablets
- -Rifampicin, isoniazid, pyrizinamide and ethambutol hydrochloride tablets
- -Saquinavir mesilate capsules
- -Stavudine capsules
- -Zidovudine capsules
- -Zidovudine oral solution
- -Zidovudine intravenous infusion
- -Zidovudine and Lamivudine tablets

-Zidovudine, Lamivudine and Abacavir tablets

New general monographs for Liquid preparations for oral use and Oral powders are included to support the relevant specific dosage-form monographs. The monograph for Liquid preparations for oral use highlights that such preparations are often the dosage form of choice for paediatric use. This general monograph also includes a statement on Safety concerns in the section on *Manufacture*. This draws attention to the importance of ensuring the quality of starting materials. Failure to ensure that starting materials are of the required quality can have very serious consequences. The most documented incidents involve liquid preparations for oral use manufactured with excipients such as glycerol and propylene glycol that have been contaminated, adulterated or mixed up with diethylene glycol. Such incidents have been responsible for hundreds of deaths (through kidney failure) throughout the world.

Many of the new monographs introduced into this supplement of *The International Pharmacopoeia* are for specific dosage forms. An important function of these monographs is to provide an independent analyst with some means of demonstrating the quality of a product in relation to impurities. Guidance notes concerning the application of tests for related substances to dosage-form monographs have been published and are also provided within the section on Supplementary information. Developing suitable pharmacopoeial tests, especially for preparations containing several active ingredients or with complex formulations, can present challenges. This aspect of dosage-form monographs continues to evolve and an approach to dealing with complex liquid formulations is illustrated by the test in the monograph for Zidovudine oral liquid.

Revision. In parallel with the development of the new monograph for Doxycycline capsules, the published monographs for Doxycycline hyclate and Doxycycline tablets have been revised.

A requirement for dissolution has been included in the above monographs for Doxycycline capsules and tablets and added to a number of other monographs for tablets and capsules containing highly soluble drug substances, for example, Chloroquine sulfate tablets and Isoniazid tablets. A standardized dissolution test has been included in these monographs as an alternative to disintegration since, for pharmacopoeial purposes, the disintegration test is considered to be generally satisfactory for such products.

Revision of storage statements in monographs for substances and dosage forms has been carried out in order to remove references to in "in a cool place" or "at a temperature not exceeding 15 °C", wherever possible. This has been done in recognition of the impracticality of continuing to recommend a maximum storage temperature of 15 °C. In the past ”a cool place” was a term used fairly widely in pharmacopoeias. A cool place was normally understood to mean a temperature below 15 °C – typically, in temperate regions, the unheated larder/pantry in a house built before the mid-20th century. Once storage in a refrigerator provided a temperature range of 2° to 8°, a cool place was usually taken to correspond to a temperature range of 8° to 15 °C. The revised statements either make no reference to a storage temperature thereby implying, in accordance with the *General Notices*, that storage at room temperature is suitable or, where necessary (for example, for Colecalciferol), specify a temperature between 2° to 8 °C.

Methods of analysis. General methods of analysis that are commonly used in carrying out the tests and assays included in the monographs of *The International Pharmacopoeia* are described in the section on *Methods of Analysis*. As was noted in the *Preface* to the main volumes published in 2006, in some cases a specific cross-reference to the method required was provided within the monograph text. However, in other cases, where the relevant method could be inferred from the title of the test (for example, Specific optical rotation, Sulfated ash) no explicit cross-reference was given. It was noted that a statement had been added to the General notice on *General requirements* to assist in the correct interpretation of the monograph requirements, especially in those cases where there is no cross-reference. This statement emphasizes that, whether or not a specific cross-reference is included, the requirements of the monographs of *The International Pharmacopoeia* are to be interpreted in relation to the relevant method of analysis. In the interests of improved transparency, a specific cross-reference has been given within the monographs published in this supplement in all cases where a general method text is available. Such cross-references are usually in the form of the number of the method text given in parentheses, for example "(1.13)" for the method text for "Determination of pH".

Infrared reference spectra. Many monographs in *The International Pharmacopoeia* include an identification test using infrared spectroscopy; these tests usually allow comparison either with a spectrum obtained from the International Chemical Reference Substance (ICRS) or with a reference spectrum. Until now, these spectra were held by the WHO Collaborating Centre in Sweden and the user of the pharmacopoeia, who wished to make use of a reference spectrum rather than prepare a spectrum using the ICRS, had to obtain the required infrared reference spectrum from the Collaborating Centre. To avoid any such inconvenience the majority of the infrared reference spectra required are now published within this supplement.

Chromatographic tests. In chromatographic tests included within the monographs of *The International Pharmacopoeia*, the type of chromatographic column, column packing or thin-layer chromatography (TLC) plate to be used is stated but reference to commercial sources of these supports is not given. When a draft monograph is circulated for comment, the particular column that was used during the development of a liquid chromatographic test is provided for information (usually in a footnote to the text). This information is now provided on the WHO Medicines website to assist analysts with respect to choice of column for those monographs recently introduced into the pharmacopoeia.

It is emphasized that this information is intended to indicate a commercially available material that has been found to be suitable but does not imply that a different but equivalent commercial brand may not be used. Whatever column is chosen, the analyst is responsible for ensuring that the chromatographic system achieves the desired separation as defined by the system suitability/validity requirements of the monograph.