WHO Drug Information

Contents

WHO Prequalification of Medicines Programme

Collaborative participation of national inspectors in WHO prequalification 201
WHO Prequalification of Medicines Programme: inspection news report 205

Biomedicines and Blood Products

WHO biological reference preparations for Chagas disease diagnostic tests 208

Safety and Efficacy Issues

Rotavirus vaccines update 210
Earlier detection with EudraVigilance 210
Quinine sulfate: risk evaluation for haematological reactions 211
Daptomycin: eosinophilic pneumonia 211
ENCePP: risk/benefit of medicines 212
Sodium valproate and carbapenems: interaction 212
Leflunomide: risk of severe liver injury 212
Methylnaltrexone bromide: gastro-intestinal perforation 213
Levonorgestrel-releasing intrauterine system: uterine perforation 213
Pregabalin: suicidal ideation 214

Regulatory Action and News

Dextropropoxyphene: withdrawal 216
Bazedoxifene: withdrawal of marketing authorization application 217
Gemtuzumab ozogamicin: voluntary withdrawal 217
Ceftobiprole medocaril for injection: discontinuation 217
International chemical reference substances: EDQM and WHO collaborate 218

ATC/DDD Classification

ATC/DDD Classification (temporary) 218
ATC/DDD Classification (final) 221

Consultation Document

The International Pharmacopoeia

Amoxicillin oral suspension 224
Artesunate for injection 226
Didanosine capsules 230
Efavirenz tablets 234
Mefloquine tablets 237
Metronidazole oral suspension 242
Oseltamivir capsules 244
Sodium bicarbonate intravenous infusion 247
Sulfadoxine and pyrimethamine tablets 248
Sulfamethoxazole and trimethoprim tablets 252

Recent Publications, Information and Events

Restricted and banned pharmaceuticals 257
Hands-on approach to pharmaceutical policy 257
Certification programme for WHO Drug Dictionary 257
New WHO quality assurance guidelines 258
Good procurement practices for ACTs 258

Recommended International Nonproprietary Names

List 64 259

Announcement

The 14th International Conference of Drug Regulatory Authorities (ICDRA) will be hosted by the Health Sciences Authority, Singapore, in collaboration with the World Health Organization

The ICDRA will take place in Singapore from 30 November to 3 December 2010

Updated information is available at:
http://www.icdra2010.sg
http://www.who.int/medicines/icdra

WHO Prequalification of Medicines Programme

Collaborative participation of national inspectors in WHO prequalification

The objective of the WHO Prequalification of Medicines Programme is to cooperate with national medicines regulatory agencies (NMRAs) to comprehensively evaluate the quality, safety and efficacy of medicinal products based on information submitted by manufacturers and to inspect the corresponding manufacturing and clinical sites. The Programme currently focuses on products for the treatment of HIV/AIDS, malaria, tuberculosis, reproductive health and selected individual products for other diseases such as oseltamivir (management of influenza) and zinc sulphate (management of acute diarrhoea in children).

Increasingly, key strategies of the Programme focus on collaboration and capacity building for inspectorate staff to support sustainable evaluation and monitoring of the quality of medicines used in countries where prequalified medicines are produced and/or sold. Normally, each WHO prequalification inspection is conducted by a WHO inspector, a co-inspector from one of the Pharmaceutical Inspection Cooperation Scheme (PICS) member countries, an observer from the NMRA of the host country and, in some cases, an observer from an NMRA of a potential recipient country of products.

These collaborative and capacity building activities have also become effective catalysts for harmonization of medicines regulation in countries not being constituencies of the International Conference on Harmonization (ICH). Collaboration and capacity building has also been requested by NMRAs through the recommendations made at the International Conferences of Drug Regulatory Authorities (ICDRA). (See: http://www.who.int/medicines/icdra).

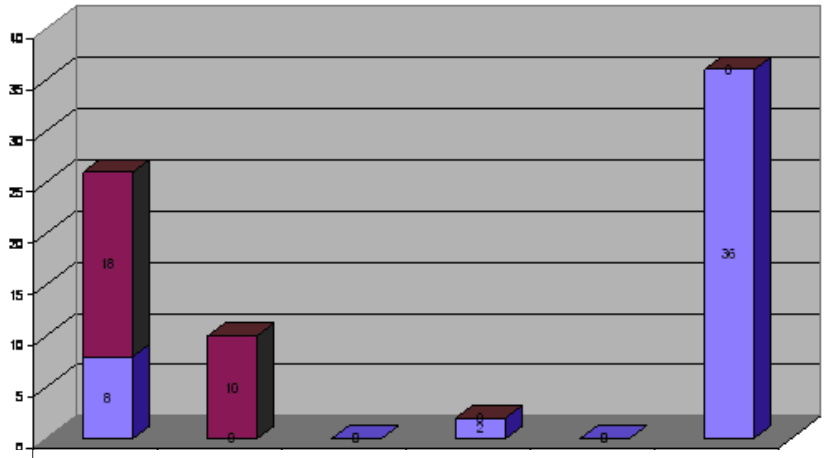
Elements of capacity building and collaboration

Encouraged by feedback from these activities, the Programme has embarked on strengthening its capacity building strategy. This strategy targets increased involvement of inspectors from NMRAs of developing countries and other interested Member States in inspections organized by the WHO Prequalification of Medicines Programme (including joint inspections) and better sharing of inspection-related information. It has the following objectives:

- Inspection-related capacity building in NMRAs of developing and other interested countries.
- Facilitating use of WHO prequalification inspection results in the national regulatory environment for information and decision making.
- Facilitation of harmonization through joint inspections and sharing of outcomes.
- Workload sharing and promotion of methods to avoid duplicate inspections.

These activities will be undertaken in a collaborative manner. Nominated inspectors from NMRAs of developing and other interested countries will be invited to participate in WHO-organized inspections and, in turn, NMRAs will be given appropriate access through a secure website to the outcome of these inspections.

Figure 1. Source of observers by WHO Region: January 2008 — April 2010



	AFR	AMR	EMR	EUR	SEAR	WPR
From other country	18	10	0	0	0	0
From host country	8	0	0	2	0	36

Within this collaborative procedure, NMRAs may share their inspection plans and nominate inspectors to participate as observers or co-inspectors in the WHO prequalification inspections, including other joint inspections arranged between participating countries. The Programme will allocate nominated inspectors to scheduled inspections with consideration as to their qualifications, experience and expressed interest in the site as indicated in the shared NMRA inspection plan. Consideration will be given to inspectors who may represent several countries through harmonization initiatives, but equal opportunity will be accorded to participating NMRAs/countries. (More detailed information is available at www.who.int/prequal.)

Collaborative procedure for inspections

A collaborative procedure has been established in line with the mission and strategy of the WHO Prequalification of Medicines Programme and in response to country needs. National regulatory authority collaboration and capacity building is an integral part of the Programme's mission. Its strategy is to:

- Apply unified standards of acceptable quality, safety and efficacy.
- Comprehensively evaluate the quality, safety and efficacy of medicinal products based on information submitted by the manufacturers and inspection of the corresponding manufacturing and clinical sites.
- Prequalify quality control laboratories of pharmaceuticals.
- Capacity building of human resources from national regulatory authorities, including inspectorates and quality control laboratories, and from manufacturers in developing countries, to ensure medicines quality.

Participation

Any NMRA of a WHO Member State can express an interest to collaborate with the WHO Prequalification of Medicines

Programme inspection activities. NMRAs of developing countries and/or of countries participating in harmonization initiatives of regulatory activities are particularly encouraged to participate in supporting capacity building.

Participation in the prequalification procedure is voluntary. However, WHO reserves the right to prioritize collaboration with:

- NMRAs having an urgent need and commitment for capacity building.
- NMRAs in regions pursuing harmonization of their regulatory activities.
- NMRAs belonging to the PIC/S providing substantial support in terms of making their inspectors available to WHO as co-inspectors.

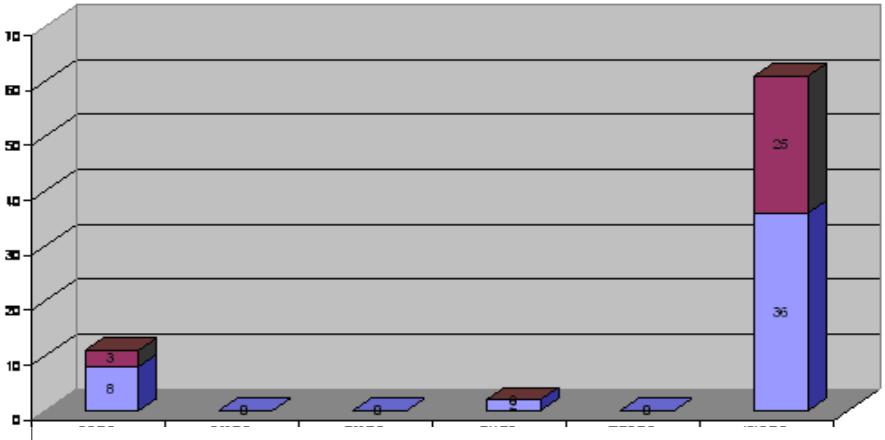
NMRA participation in the collaborative procedure for inspections
Any NMRA wanting to participate in the Procedure should provide WHO with:

1. A letter expressing interest in participating in the WHO Collaborative Procedure for Inspections and confirming that the submitted information is complete and correct.

2. Information on the NMRA, compiled in the prescribed format:

- Name and contact address of the head of the NMRA.
- Name and contact details of the focal point for inspections. The focal point will moderate access and postings to a secure website especially created within the WHO website for that purpose.
- Names, qualifications (basic and specialized training in good manufacturing practices) and experience in years, numbers and categories inspected (e.g., oral solid dosage forms, oral and external liquids and mixtures, sterile injectables, contact research organizations) of NMRA inspectors. A nominated inspector should:

Figure 2. Location of inspection site by WHO Region where an observer participated: January 2008 — April 2010



	AFR	AMR	EMR	EUR	SEAR	WPR
From other country	3	0	0	0	0	25
From host country	8	0	0	2	0	36

- be a person already appointed as an inspector in the NMRA;
- have appropriate qualifications and basic experience in inspection;
- have good knowledge of WHO good manufacturing practices (GMP), good clinical practice (GCP) and good laboratory practice (GLP) and related norms and standards as appropriate for the intended inspection;
- have a good command of English and be able to follow the inspection in English;
- have good interpersonal skills;
- have no conflict of interest and willing to sign a confidentiality agreement;
- be willing and able to travel to other countries;
- be able and in a position to share the acquired skills with colleague inspectors in the NMRA and/or region.

• Inspection schedule in the prescribed format.

• If the inspectorate of the NMRA has documented its quality system as a Quality Manual, this can be submitted.

All of the above-mentioned information should be submitted in English. Submissions that are not made in English must be accompanied by a certified English translation.

Depending on the circumstances, this may be piloted in one of the regional groupings of developing countries which has initiated harmonization activities.

Guidelines and standards used
WHO norms and standards for GMP, GCP and GLP are the basis for inspections, together with other relevant international guidelines. WHO prequalification inspection procedures will be used in arranging inspections in a way which enables involvement of nominated inspectors from concerned NMRAs. WHO coordinates these inspections and has responsibility for inspection within the collaborative procedure.

Results of the inspection
Communication of conclusions reached following an inspection remains a prerogative of the national inspectorate and neither is it mandatory for another inspectorate to accept the outcome. For example, a participating NMRA may reach a conclusion which is different from that of WHO as a result of risk analysis concerning a national situation.

Nevertheless, it is hoped that the outcomes of a collaborative inspection will be utilized by concerned authorities for the purpose of building regulatory capacity, saving resources, acceleration of national medicines registration and as a complement to national quality assurance measures.

Issues of confidentiality and conflict of interest
All members of staff in the prequalification team are bound by a confidentiality agreement. Appointed experts also have to treat information submitted and observed during site inspections as strictly confidential and proprietary to WHO or parties collaborating with WHO in accordance with the terms contained in the agreement.

Before participating in a collaborative procedure, the nominated focal point and each nominated observer or co-inspector are invited to sign a confidentiality agreement and declaration of interest as an expert adviser to WHO.

Expressions of Interest
Submissions containing the covering letter and the completed expression of interest form should be sent to the Prequalification of Medicines Programme, HSS/EMP/QSM, World Health Organization, 1211 Geneva 27, Switzerland.

Expected benefits and advantages
It is hoped that the collaborative procedure will lead to multiple benefits. These may include capacity building of national inspectorates, particularly those in developing countries, through hands-on training in inspection, practical interpretation and the application of international norms and standards. Participating inspectors are encouraged to develop similar skill levels, similar approaches to inspection and practical experience in multi-agency collaboration which will in turn facilitate harmonization of regulatory practices in the region. This will also lead to faster access to good quality essential medicines, including those prequalified by WHO. Such an approach and skills may then be used to facilitate harmonized inspections among regional NMRAs including for product categories outside the focus of the Programme.

Conclusion
Participation in inspections of the Programme has tangible benefits in capacity building for NMRAs and in facilitating harmonization. The collaborative procedure encompasses strategies and incentives to encourage commitment to improve inspection quality, systems and outcomes. It should be embraced by all wishing to improve regulatory systems and harmonization and will lead to the provision of better quality medicines in WHO Member States, particularly in developing countries.

WHO Prequalification of Medicines Programme: inspection news report

The inspection team of the WHO Prequalification of Medicines Programme has launched a news report service to communicate developments and activities that may be of interest to manufacturers, contract research organizations (CROs) and other interested parties. Reports are published regularly on the WHO Prequalification of Medicines Programme web site at www.who.int/prequal

Related Expert Committee work
Among the activities of the Expert Committee on Specifications for Pharmaceutical Preparations, several informal consultations have taken place in the last three months where various proposed new guidelines have been discussed (See also http://www.who.int/medicines). These cover good manufacturing practices (GMP) for microbiological laboratories, quality risk management and a guideline on artemisinin used as a starting material in the production of active pharmaceutical ingredients. Various comments have subsequently been received and these are now being considered.

The Forty-fourth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations was recently published in the *Technical Report Series* (TRS 957) (http://www.who.int/publications). It contains new and revised guidelines including:

- Good practices for pharmaceutical quality control laboratories.
- Good manufacturing practices (GMP) for active pharmaceutical ingredients (APIs). This guideline now mirrors the ICH Q7 Guidelines. The WHO Prequalification of Medicines Programme has been using the ICH Q7 text as a reference for a considerable time.
- GMP for pharmaceutical products containing hazardous substances. This guideline was initially developed as additional GMP guidance focusing on recommendations appropriate to manufacture of products containing hor-

mones. The guideline has undergone considerable change as a result of numerous comments and the scope has been expanded.

- Good Distribution Practices.

- GMP for sterile products. The WHO GMP text for sterile products has been revised to ensure it is up to date with current developments to better harmonize global norms and standards. Some questions have arisen from the new text, especially in relation to paragraph 4.6.2. which is now under discussion, and clarification will soon be provided as to interpretation of this section.

- Guidelines for the preparation of a Contract Research Organization (CRO) Master File (CROMF) in the framework of the WHO Prequalification of Medicines Programme. CROs will now be requested to submit a master file (similar to a site master file) to WHO if a study was conducted at a site listed in a product dossier. The CROMF provides general information about the activities on site and inspectors will use it as background information during preparation and planning of inspections. It can also be a useful tool for national medicines regulatory authorities which conduct inspections at CROs.

- Annex 6 of TRS 957 further contains guidelines on the prequalification of product dossiers.

Inspections, meetings and consultations

During the period April–June 2010, the following inspections have been performed by the WHO Prequalification of Medicines Programme.

- South Africa. A site for finished pharmaceutical preparations (FPPs) was considered to be operating at an acceptable level of compliance with GMP.

- India. Two CROs for the clinical section of a bioequivalence study.

- India. One company for bio-analysis of bioequivalence studies.

WHO Public Inspection Reports (WHO PIRS) will be published shortly for these inspections and can be accessed on the Programme's web site at http://www.who.int/prequal.

- Two inspections were also conducted in Africa and one in China for FPPs.

- China. One inspection to assess CRO compliance with GCP and GLP.

Inspectors from the programme also participated in informal consultations on GMP guidelines. A training workshop on pharmaceutical development focusing on paediatric medicines was held in China 21–24 June 2010. This was attended by 50 participants from national medicines regulatory authorities and industry from China, Hong Kong SAR, Indonesia, Republic of Korea, Thailand and Viet Nam. (The report is posted at http://www.who.int/prequal).

Two inspectors from the Programme provided training to inspectors in a workshop in Ethiopia, and one also attended a workshop in Geneva presented by Médecins Sans Frontières on improving access to quality medicines for use in resource-limited settings.

An invitation has been extended to inspectors from NMRAs in developing countries and other interested Member States to take part in inspections organized by the WHO Prequalification of Medicines Programme, including joint inspections and sharing of inspection related information within a collaborative procedure on inspection. Three countries from the East African Community (EAC) have so far expressed an interest to participate in this procedure.

The WHO Prequalification of Medicines Programme also organized a workshop in Copenhagen in July 2010 for manufacturers already participating or interested in participating in prequalification activities. The meeting presented an opportunity to hear about common dossier and GMP deficiencies and new or revised WHO guidelines from expert assessors, inspectors and other manufacturers. There was also an opportunity to discuss experience with the WHO Prequalification of Medicines Programme and help identify possible opportunities for improvement. The focus of the meeting was on multisource (generic) medicines since innovative medicines are prequalified based on scientific assessments carried out by stringent authorities such as the European Medicines Agency or the US Food and Drug Administration. An interactive style of meeting was proposed, with presentations, panel discussions and workshops. More details of workshop outcomes is available at http://www.who.int/prequal

Biomedicines and Blood Products

WHO biological reference preparations for Chagas disease diagnostic tests

A core function of the World Health Organization (WHO) as set out in Article 2 of its Constitution is to "develop, establish and promote international standards with respect to food, biological, pharmaceutical and similar products" and "to standardize diagnostic procedures as necessary". Biological products, as defined by WHO, comprise a class of substances used in medicine derived from living sources ranging from normal or genetically modified organisms to human tissues and used in the diagnosis, treatment or prevention of disease. In practice, biological products cover vaccines, blood and blood products, biological therapeutics and *in vitro* biological diagnostic devices.

WHO develops and establishes International Biological Reference Standards and Reference Panels (physical standards) which form the basis for comparison of results between different biological assays, facilitate transfer of laboratory science into worldwide clinical practice and support harmonization of international quality and safety regulations. A list of the WHO Biological Reference Standards and Panels is available at http://www.who.int/bloodproducts/catalogue

Coordinated by a Secretariat at WHO Headquarters, work is developed through an Expert Committee on Biological Standardization, with the assistance of the WHO Collaborating Centres for Biological Standards and Standardization and the support of WHO Working Groups and Consultations on specific topics.

During WHO Consultations on International Biological Reference Preparations for Chagas disease Diagnostic Tests at WHO Geneva in 2007 and 2009, participants supported the development of a WHO International Biological Reference Panel for Chagas disease diagnostic tests based on the detection of antibodies to *Trypanosoma cruzi.* Representatives of reference and clinical laboratories, blood establishments, regulatory agencies and manufacturers of diagnostic tests participated at these consultations. The composition, intended use and production of a global reference panel and the design of an international collaborative study to calibrate the proposed reference panel and the tests and technologies to be considered in the WHO collaborative study were discussed.

Two main *T. cruzi* groups have been identified in endemic regions as T. cruzi I and T. cruzi II and published reports indicate different reactivity of sera from patients living in the region where T. cruzi I is prevalent, when measured by tests made from T. cruzi II antigens. For this reason, the second consultation proposed the development of a panel of two positive preparations (defibrinated plasma) representing the T. cruzi I and T. cruzi II groups, respectively, to facilitate the control of analytical sensitivity of commercial tests in all regions. No borderline positive or negative control sample would be needed. There was also consensus on using samples of medium reactivity in order to distinguish between tests that use poor quality reagents. It is expected that preparations in the panel should be detected by all the commercially available approved tests.

Confirmation of the *T. cruzi* genotype from infected donors remains difficult for various reasons:

- Serology cannot be used to identify the genotype of the infecting strain.
- Parasitaemia in blood donors is usually low.
- Additional ethical approval is required for isolation/detection of the parasite. Nevertheless, a recommendation was made to urge efforts to isolate parasites from the donors involved.

The concentration of antibodies in chronically infected people is usually high and can be demonstrated by conventional tests which include the indirect immunofluorescence assay (IFA), the indirect haemagglutination assay (IHA) and the enzyme-linked immunosorbent assay (ELISA). Some of these tests use crude antigen preparations, others use recombinant or synthetic antigens. Other tests recently developed include combinations of recombinant proteins, synthetic peptides or purified antigens as well as rapid diagnostic tests. Both screening tests and confirmatory tests will be considered in the collaborative study.

The reactivity of the above proposed candidate preparations has been assessed in a pilot study including various EIAs, IFA, IHA and confirmatory tests such as radio immuno precipitation assay (RIPA), Immunoblot and Tesa Blott in a pilot study. A WHO Collaborative study to evaluate the suitability of the above proposed candidate preparations will follow involving a wide number of tests and 25 laboratories from regulatory agencies, investigation laboratories, blood donor screening laboratories and diagnostic laboratories of the WHO American, European and Western Pacific Regions.

Overall, the WHO Project on International Biological Reference Preparations for Chagas Disease Diagnostic Tests is a key element to implementing access to quality diagnosis of Chagas disease worldwide. The availability of internationally agreed reference preparations will contribute to facilitating control of the analytical sensitivity of in-house tests and commercially available kits by test developers, manufacturers, regulators, blood establishments, reference, and diagnostic laboratories. This will strongly contribute to the harmonization of international regulations and facilitation of development of new tests.

References

1. World Health Organization. Recommendations for the preparation, characterization and establishment of international and other biological reference standards (revised 2004): Annex 2, *Technical Report Series*, No 932. 2005.

2. Report of the WHO Consultation on Global Measurement Standards and their use in the in vitro biological diagnostic field. WHO Geneva, June 2004. http://www.who.int/bloodproducts/ivd/infectious_markers

3. First WHO Consultation on International Biological Reference Preparations For Chagas Diagnostic Tests. http://www.who.int/bloodproducts

4. Second WHO Consultation on International Biological Reference Preparations For Chagas Diagnostic Tests. http://www.who.int/bloodproducts

Safety and Efficacy Issues

Rotavirus vaccines update

New Zealand — In May this year the manufacturer of the rotavirus vaccine, RotaTeq®, informed Medsafe that DNA fragments of both PCV–1 and PCV–2 had been identified in the vaccine. This follows an alert in March this year that PCV-1 virus had been found in Rotarix® vaccine.

There is no evidence to suggest that the presence of DNA fragments of PCV–1 and PCV–2 in rotavirus vaccines poses a safety concern for patients. PCV–1 and PCV–2 are types of porcine circovirus and are composed of a single strand of DNA. These viruses are commonly found in pigs; although PCV–2 may cause illness in pigs neither virus is known to cause illness in humans.

Having considered relevant scientific information, Medsafe has concluded that the continued use of both rotavirus vaccines is supported by the weight of current evidence of safe use of these vaccines. This advice is consistent with the views of the US Food and Drug Administration and the Australian Therapeutic Goods Administration (TGA).

Medsafe advises prescribers to have a balanced discussion with people who are seeking rotavirus vaccination for their children. Discussing the potential benefits of the vaccine and any theoretical risks associated with PCV will help them to make an informed decision (1, 2).

References

1. Allan G, Ellis JA. Porcine circoviruses: a review. *Journal of Veterinary Diagnostic Investigation*, **12**:3–14.

2. Tham KM, Hansen M. 2003. Detection of porcine circovirus types 1 and 2 in abattoir-slaughtered pigs in New Zealand. *Surveillance*, **30**(1): 3–5.

3. Update on rotavirus vaccines. *Prescriber Update*, 2010;**31**(2):14

Earlier detection with EudraVigilance

European Union — An evaluation of the use of the European Medicines Agency's statistical signal detection method in the adverse drug reaction data collected in the EudraVigilance database has shown a significantly earlier detection of drug safety issues in about 54% of cases where a clinically important adverse drug reaction report was found (compared to routine pharmacovigilance).

The study (1) was carried out by the European Medicines Agency and was conducted in relation to centrally authorized medicines. It provides direct evidence for a strong additive role of Eudravigilance signal detection methods. The study also underlines the importance of established pharmacovigilance systems such as active surveillance, clinical trials or periodic safety update reporting, and concludes that a combination of routine pharmacovigilance and statistical signal detection provides optimal safety monitoring with earlier detection and better management of safety issues, thereby improving the protection of public health.

EudraVigilance is the European Union database for adverse drug reaction reports. It provides a single repository for all spontaneous reports of suspected serious adverse reactions concerning

medicines that are authorized in the European Union received via the national competent authorities for medicines regulation and the pharmaceutical industry.

References

1. Alvarez Y., Hidalgo A., Maignen F. et al. Validation of Statistical Signal Detection Procedures in EudraVigilance Post Authorization Data: a retrospective evaluation of the potential for earlier signalling. *Drug Safety,* 2010; **33**(6):475–487.

2. *European Medicines Agency Press Release*, EMA/319375/2010, 25 May 2010, http://www.ema.europa.eu

Quinine sulfate: risk evaluation for haematological reactions

United States of America — Due to continued reports of serious side effects in patients using Quinine sulfate (Qualaquin®) "off-label" for night-time leg cramps, the Food and Drug Administration (FDA) has approved a risk management plan to warn against the use of this drug for such unapproved uses.

Qualaquin® should not be used for night time leg cramps. Its use may result in serious and life-threatening haematological reactions, including serious bleeding due to thrombocytopenia and haemolytic-uraemic syndrome/thrombotic thrombocytopenic purpura, which in some cases may result in permanent kidney damage. In some patients, adverse reactions result in hospitalization and death.

Qualaquin® is approved for the treatment of uncomplicated malaria caused by the parasite *Plasmodium falciparum*, primarily in travellers returning from malaria-endemic areas.

Reference: *FDA Drug Safety Communication*, 8 July 2010 at http://www.fda.gov/MedWatch/report.htm

Daptomycin: eosinophilic pneumonia

United States of America — The Food and Drug Administration (FDA) has informed patients and healthcare professionals of the potential for developing eosinophilic pneumonia during treatment with daptomycin (Cubicin®), an intravenous antibacterial drug.

Daptomycin was first approved in September 2003 to treat serious skin infections. In 2006, it was approved to treat bloodstream infections.

Eosinophilic pneumonia is a rare but serious condition. Symptoms include fever, cough, shortness of breath and difficulty breathing.

In 2007, pulmonary eosinophilia was added to the Adverse Reactions, Post-Marketing Experience section of the Cubicin® product label. Since then, the Agency has reviewed published case reports of associated eosinophilic pneumonia, (1–4) and conducted a review of post-marketing adverse event reports from the FDA's Adverse Event Reporting System (AERS). FDA's review identified seven cases of eosinophilic pneumonia between 2004 and 2010 that were most likely associated with Cubicin®.

Based on these reviews, FDA determined that eosinophilic pneumonia can be associated with daptomycin use and requested that the manufacturer include this information in the Warnings and Precautions and Adverse Reactions, Post-Marketing Experience sections of the drug label.

References

1. Lal Y, Assimacopoulos AP. Two cases of daptomycin-induced eosinophilic pneumonia and chronic pneumonitis. *Clin Infect Dis.* 2010;**50**:737-40.

2. Hayes D Jr, Anstead MI, Kuhn RJ. Eosinophilic pneumonia induced by daptomycin. *J Infect.* 2007;**54**:e211-3.

3. Miller BA, Gray A, Leblanc TW, Sexton DJ, Martin AR, Slama TG. Acute eosinophilic pneumonia secondary to daptomycin: a report of three cases. *Clin Infect Dis.* 2010;**50**:e63-8.

4. Kakish E, Wiesner AM, Winstead PS, Bensadoun ES. Acute respiratory failure due to daptomycin induced eosinophilic pneumonia. *Respir Med CME.* 2008;**1**:235-7.

5. *FDA Drug Safety Communication*, 29 July 2010, at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm220273.htm

ENCePP: risk/benefit of medicines

European Union — The European Medicines Agency and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) has launched 'ENCePP studies'. Building on the foundations of the ENCePP network of Excellence, 'ENCePP studies' is a seal for EU-based, benefit/risk or risk studies that are carried out in compliance with the ENCePP code of conduct for independence and transparency and its methodological research standards and are entered into a publicly available electronic register before their start.

Investigators who apply to conduct an ENCePP study commit to a maximum level of transparency with respect to relevant information regarding their investigation. This includes publication of study findings regardless of their positive or negative results and making public relevant information on the study protocol before the study commences.

The seal 'ENCePP studies' is a confirmation for the public that the study was conducted in adherence with ENCePP research and methodological principles and will increase trust in the robustness of the findings.

Reference: *European Medicines Agency Press Release*, EMA/343605/2010, 11 June 2010 at http://www.ema.europa.eu

Sodium valproate and carbapenems: interaction

New Zealand — Prescribers are reminded of the clinically significant interaction between carbapenem antibiotics (such as imipenem, meropenem and ertapenem) and sodium valproate. Although this interaction is well established, international reports suggest it is more severe than initially thought.

The interaction has been reported to result in a 60–100% decrease in valproate plasma concentration within two days and reduced therapeutic effect. The underlying mechanism of action is yet to be explained (1).

Monitoring valproate plasma levels or adjusting the dose is unlikely to manage this interaction given its extent and rapid onset. Prescribers are therefore advised to avoid the use of carbapenem antibiotics in patients taking sodium valproate.

References

1. European Medicines Agency. 28 January 2010. Monthly Report – Pharmacovigilance Working Party, January 2010 Plenary Meeting. http://www.ema.europa.eu/pdfs/human/phvwp/3313810en.pdf

2. Sodium valproate and carbapenems — Interaction. Prescriber Update, 2010; **31**(2):14

Leflunomide: risk of severe liver injury

United States of America — The Food and Drug Administration (FDA) has provided patients and healthcare professionals with information on severe liver injury involving leflunomide (Arava®),

used to treat rheumatoid arthritis. The FDA previously required a Boxed Warning stating that leflunomide was contraindicated in pregnant women, or women of childbearing potential who were not using reliable contraception.

The decision to add information on severe liver injury to the Boxed Warning was based on the FDA's review of adverse event reports which identified 49 cases of severe liver injury, including 14 cases of fatal liver failure, between August 2002 and May 2009. In this review, the greatest risk for liver injury was seen in patients taking other drugs known to cause liver injury, and patients with pre-existing liver disease.

The information on severe liver injury being added to the Boxed Warning states:

- Patients with pre-existing liver disease should not receive leflunomide.
- Patients with elevated liver enzymes (ALT greater than two times the upper limit of normal) should not receive leflunomide.
- Caution should be used in patients who are taking other drugs that can cause liver injury.
- Liver enzymes should be monitored at least monthly for three months after starting leflunomide and at least quarterly thereafter.
- If the ALT rises to greater than two times the upper limit of normal while the patient is on leflunomide – leflunomide should be stopped, cholestryamine washout begun to speed the removal of leflunomide from the body and follow-up liver function tests conducted at least weekly until the ALT value is within normal range.

Reference: *FDA Drug Safety Communication*, 13 July 2010 at http://www.fda.gov/MedWatch/report.htm

Methylnaltrexone bromide: gastrointestinal perforation

Canada — The manufacturer of methylnaltrexone bromide (Relistor® Subcutaneous Injection) has provided important new safety information.

Methylnaltrexone bromide is indicated for the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care. When response to laxatives has been insufficient, methylnaltrexone bromide is used as an adjunct therapy to induce a prompt bowel movement. Patients with advanced illness may be at increased risk of gastrointestinal (GI) perforation if they have conditions associated with localized or diffused reduction of structural integrity in the GI wall. The risks and benefits of Relistor® treatment should be weighed for each patient.

Reference: *Health Canada Health Advisory*, 28 July 2010 at http:www.healthcanada.gc.ca/medeffect

Levonorgestrel–releasing intrauterine system: uterine perforation

Canada — The manufacturer of Mirena® has reminded health care professionals of important safety information regarding reports of uterine perforation. Mirena® is a levonorgestrel-releasing intrauterine system approved for conception control up to a maximum of 5 years and for treatment of idiopathic menorrhagia following appropriate diagnostic investigation in women.

Uterine perforation is a rare, but serious complication associated with intrauterine contraceptive devices. The risk of perforation may be increased with use in the post-partum period, during lactation, and in women with an atypical uterine anatomy (such as fixed retroverted uterus).

In order to minimize the risk of complications, health care professionals are encouraged to:

- Ensure they are familiar with and/or trained on the correct insertion technique for Mirena® and carefully review the insertion instructions included in the labelling.
- Consider performing ultrasound or X-ray imaging in case of a difficult insertion, if patients complain of pain, or if there is suspicion that the system may not be correctly positioned.
- Follow up patients 4 to 12 weeks after insertion and once a year thereafter or more frequently, as required.
- Inform patients before the procedure about the risk of uterine perforation, especially in the post-partum period and during lactation, and educate them on possible signs of this complication, including, but not limited to, severe low abdominal pain which may be associated with bleeding after the procedure. Advise the patient how to self-check the removal threads of Mirena®.

Reference: *Health Canada Health Advisory*, 15 June 2010 at http:www.healthcanada.gc.ca/medeffect

Pregabalin: suicidal ideation

Canada — Health Canada has received 16 reports of suicidal ideation and one report of suicide attempt suspected of being associated with the use of pregabalin (Lyrica®). The Canadian product monograph for Lyrica® lists suicide attempt under "less common clinical trial adverse drug reactions" and describes it as being infrequent.

Seven of the 16 cases included a positive dechallenge, and one case included a positive rechallenge. Pregabalin has analgesic, anti-epileptic and anxiolytic activity (1). Marketed in Canada since July 2005, pregabalin is indicated for the management of neuropathic pain associated with diabetic neuropathy, post-herpetic neuralgia and pain associated with fibromyalgia in adults, and it may be useful in the management of central neuropathic pain. The Canadian product monograph for Lyrica lists suicide attempt under "less common clinical trial adverse drug reactions" and describes it as being infrequent (1). Patients with chronic pain are at increased risk of depression, which may lead to suicidal ideation and attempt, so the indication for taking pregabalin in these patients may also be a confounding factor (2).

In the United States, pregabalin is also indicated as adjunctive therapy in adults with partial onset seizures (3). It is not approved for this indication in Canada. In December 2008 and April 2009, the US Food and Drug Administration communicated safety notices concerning the increased risk of suicidal behaviour and ideation in patients taking anti-epileptic drugs, including pregabalin, for any indication (4, 5).

Extracted from Canadian Adverse Reaction Newsletter, Volume 20(3), July 2010

References

1. Lyrica (pregabalin) [product monograph]. Kirkland (QC): Pfizer Canada Inc; 2009.

2. Gilbert JW, Wheeler GR, Storey BB, et al. Suicidality in chronic noncancer pain patients. *Int J Neurosci* 2009;**119**(10):1968-79.

3. Lyrica (pregabalin) capsules [prescribing information]. New York (NY): Pfizer Inc.; 2009.

4. Suicidal behaviour and ideation and antiepileptic drugs. Rockville (MD): US Food and Drug Administration; December 2008. http://www.fda.gov

5. Lyrica (pregabalin) capsules – detailed view: safety labelling changes approved by FDA Center for Drug Evaluation and Research (CDER). Rockville (MD): US Food and Drug Administration; April 2009. http://www.fda.gov

Regulatory Action and News

Dextropropoxyphene: withdrawal

New Zealand — Healthcare professionals are reminded that the consent to distribute dextropropoxyphene containing medicines (Capadex®, Paradex®) was revoked on 1 August 2010. From this date it is no longer legal to sell, distribute or advertise these medicines unless exempted under the Medicines Act 1981 (1). This decision follows a review by the Medicines Adverse Reactions Committee (MARC), which concluded that the risks of these medicines outweigh benefit (2). The Best Practice Advocacy Centre (bpacNZ) has issued advice for transferring patients from dextropropoxyphene (3).

Oxycodone should not be prescribed in place of dextropropoxyphene unless there has been an inadequate response to a weak opioid. Oxycodone is a strong opioid and is only indicated as an alternative to morphine on step three of the WHO analgesic ladder.

References

1. Medsafe. DHCPL dated 26 March 2010. Available at: http://www.medsafe.govt.nz/LtrtoHPCapadexandParadex.pdf

2. MARC minute item for dextropropoxyphene, December 2009. Available at: www.medsafe.govt.nz/profs/adverse/Minutes140.htm#3.1 bpacNZ. 2010.

3. Dextropropoxyphene containing medicines to be withdrawn. *Best Practice Journal*. **26**: 44. http://www.medsafe.govt.nz/profs/PUArticles/DextropropoxypheneWithdrawalReminder.htm

4. Dextropropoxyphene withdrawal – a reminder. *Prescriber Update*. 2010;**31**(2):11 at http://www.medsafe.govt.nz

Modafinil: restricted use

European Union — The European Medicines Agency has recommended restricting the use of modafinil-containing medicines which should only be used to treat sleepiness associated with narcolepsy. Doctors and patients should no longer use the medicine for the treatment of idiopathic hypersomnia, excessive sleepiness associated with obstructive sleep apnoea and chronic shift work sleep disorder.

Modafinil is a wakefulness promoting agent currently licensed in 21 countries in Europe. It is available under the following invented names: Modasomil®, Modiodal®, Provigil® and Vigil®, and as generic medicines.

A review by the Agency's Committee for Medicinal Products for Human Use (CHMP) was initiated because of a number of safety concerns, relating to psychiatric disorders, skin and subcutaneous tissue reactions as well as significant off-label use and potential for abuse. On the basis of available data, the Committee concluded that the benefits of these medicines only outweighed their risks in the therapeutic indication narcolepsy, a chronic sleep disorder characterized by excessive daytime sleepiness.

For all other indications, the Committee found that the risk for development of skin or hypersensitivity reactions and neuropsychiatric disorders outweighed the evidence for clinically important efficacy. Therefore, the Committee concluded that all other indications should be withdrawn from the marketing authorizations of these medicines.

Reference: *European Medicines Agency Press Release,* EMA/459173/, 22 July 2010 at http://www.ema.europa.eu<http://www.ema.europa.eu

Bazedoxifene: withdrawal of marketing authorization application

European Union —The European Medicines Agency has been notified by the manufacturer of its decision to withdraw its duplicate application for a centralized marketing authorization for the medicine bazedoxifene (Brilence®), 200 mg film-coated tablets. This medicine was intended to be used for the treatment of osteoporosis in postmenopausal women at increased risk of fracture.

In its official letter, the company stated that the reason for the withdrawal of the application was that no co-marketing partner had been identified prior to the CHMP opinion.

Reference: *European Medicines Agency Press Release*, EMA/342273/2010, 28 May 2010 at http://www.ema.europa.eu

Gemtuzumab ozogamicin: voluntary withdrawal

United States of America — The manufacturer of gemtuzumab ozogamicin (Mylotarg®) has announced voluntary withdrawal from the US market for patients with acute myeloid leukaemia (AML), a bone marrow cancer. The company has taken this action at the request of the Food and Drug Administration (FDA) after results from a recent clinical trial raised new concerns about the product's safety and the drug failed to demonstrate clinical benefit to patients enrolled in trials.

Mylotarg® was approved in May 2000 under the FDA's accelerated approval programme. It was approved to treat patients aged 60 years and older with recurrent AML who were not considered candidates for other chemotherapy.

At initial approval, Mylotarg® was associated with a serious liver condition called veno-occlusive disease, which can be fatal. This has increased in the post-market setting.

Reference: *FDA News Release*, 21 June 2010 at http://www.fda.gov

Ceftobiprole medocaril for injection: discontinuation

Canada — The manufacturer of ceftobiprole medocaril (Zeftera® for Injection) has informed healthcare professionals of discontinuing sale.

Ceftobiprole medocaril is currently approved for the treatment of complicated skin and skin structure infections including non-limb-threatening diabetic foot infections without concomitant osteomyelitis caused by *Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Staphylococcus aureus* (including methicillin-resistant isolates) and *Streptococcus pyogenes.*

Prescribers are advised:

- To allow all patients on the product to complete their course of therapy.
- Not to initiate treatment of new patients.

Reference: Communication from Janssen-Ortho Inc., 9 April 2010 at http:www.healthcanada.gc.ca/medeffect

International chemical reference substances: EDQM and WHO collaborate

European Union/World Health Organization — the European Directorate for the Quality of Medicines and HealthCare (EDQM) protects and promotes public and animal health in Europe. The EDQM

and the World Health Organization (WHO) are pleased to announce that EDQM is now responsible for the distribution of WHO's International Chemical Reference Substances (ICRS).

The EDQM takes over responsibility for the establishment, preparation, storage and distribution of WHO ICRS from Apoteket AB, previously the WHO Collaborating Centre for ICRS. Reference material that was held and distributed by Apoteket AB will now be distributed by the EDQM.

ICRS are adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations. They are supplied primarily for use in physical and chemical tests and assays described in the specifications for quality control of drugs published in *The International Pharmacopoeia*.

The EDQM will also organize international collaborative studies to establish new standards, when required, with WHO's assistance.

Reference: http://www.edqm.eu/en/WHO-International-Chemical-Reference-Substances-ICRS-1384.html.

ATC/DDD Classification

ATC/DDD Classification (temporary)

The following anatomical therapeutic chemical (ATC) classifications and defined daily doses (DDDs) were agreed by the WHO International Working Group for Drug Statistics Methodology 23 March 2010. Comments or objections to the decisions should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology at whocc@fhi.no. The new ATC codes and DDDs will be considered final and be included in the January 2011 issue of the ATC index. The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy. The WHO Collaborating Centre for Drug Statistics Methodology can be contacted through e-mail at: whocc@fhi.no.

ATC level	INN/Common name	ATC code
New ATC 5th level codes:		
	linagliptin	A10BH05
	taliglucerase alfa	A16AB11
	ticagrelor	B01AC24
	acetylsalicylic acid and esomeprazole	B01AC56
	dronedarone	C01BD07
	amezinium metilsulfate	C01CA25
	triamcinolone	C05AA12
	naftazone	C05CX02
	nebivolol and thiazides	C07BB12
	enalapril and nitrendipine	C09BB06
	olmesartan medoxomil, amlodipine & hydrochlorothiazide	C09DX03
	ceftaroline fosamil	J01DI02
	sitafloxacin	J01MA21
	afatinib	L01XE13
	polyplatillen	L01XA05
	eribulin	L01XX41
	albinterferon alfa-2b	L03AB12
	briakinumab	L04AC09
	voclosporin	L04AD03
	naproxcinod	M01AE18
	nimesulide	M02AA26
	idrocilamide	M02AX05
	alendronic acid, calcium and colecalciferol, sequential	M05BB05
	chondrocytes, autologous[1]	M09AX02
	retigabine	N03AX21

.../...

ATC level	INN/Common name	ATC code
	fampridine	N07XX07
	mannitol	R05CB16
	besifloxacin	S01AX23
	technetium (^{99m}) hynic-octreotide	V09IA07

1. *Chondrocytes previously classified in V03AX should be moved to the new code in M09AX02*

Change of ATC codes:

INN/common name	Previous ATC	New ATC
ephedrine	R03CA02	C01CA26[1]

1. *Only parenteral formulations*

ATC name changes

Previous	New	ATC code
dextriferron	ferric oxide polymaltose complexes	B03AB05
dextriferron	ferric oxide polymaltose complexes	B03AC01
ferric oxide dextran complex	ferric oxide dextran complexes	B03AC06
dextriferron	ferric oxide polymaltose complexes	B03AD04

New DDDs:

INN/common name	DDD	Unit	Adm.R	ATC code
tocofersolan	0.2	g[2]	O	A11HA08
C1 inhibitor	1.4	TU	P	B02AB03
dronedarone	0.8	g	O	C01BD07
amezinium metilsulfate	30	mg	O	C01CA25
tolvaptan	30	mg	O	C03XA01
lasofoxifene	0.5	mg	O	G03XC03
sitafloxacin	0.1	g	O	J01MA21
aldesleukin	0.2	mg	P	L03AC01
antithymocyte immunoglobulin (rabbit)	0.1	g	P	L04AA04
canakinumab	2.7	mg	P	L04AC08
denosumab	0.33	mg	P	M05BX04
fentanyl	0.6	mg	N	N02AB03
paliperidone	2.5	mg[3]	P depot	N05AX13
polystyrene sulfonate	45	g	O	V03AE01

2. *Expressed as tocopherol*
3. *Expressed as paliperidone*

Herbal medicinal products[4]

New DDDs:

Name	DDD	Unit	Adm.R	ATC code
Serenoa repens	0.32	g	O	G04CX02

4. Assessed and approved by regulatory authorities based on dossiers including efficacy, safety, and quality data (e.g. EU well-established use procedure).

ATC/DDD Classification

ATC/DDD Classification (final)

The following anatomical therapeutic chemical (ATC) classifications and defined daily doses (DDDs) were agreed by the WHO International Working Group for Drug Statistics Methodology in October 2009. They will be included in the January 2011 issue of the ATC index. The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy. The WHO Collaborating Centre for Drug Statistics Methodology can be contacted at whocc@fhi.no.

ATC level	INN/Common name	ATC code
New ATC level codes (other than 5th level):		
Artemisinin and derivatives, combinations		P01BF
Emergency contraceptives		G03AD
New ATC 5th level codes:		
	aliskiren and amlodipine	C09XA53
	aliskiren, amlodipine and hydrochlorothiazide	C09XA54
	amrubicin	L01DB10
	artenimol and piperaquine	P01BF05
	artesunate and amodiaquine	P01BF03
	artesunate and mefloquine	P01BF02
	artesunate and pyronaridine	P01BF06
	artesunate, sulphamethopyrazine and pyrimethamine	P01BF04
	avocado and soyabean oil, unsaponifiables	M01AX26
	belatacept	L04AA28
	belimumab	L04AA26
	bilastine	R06AX29
	bismuth subcitrate, tetracycline and metronidazole	A02BD08
	bisoprolol and other antihypertensives	C07FB07
	chlormadinone and estrogen	G03AA15
	choline fenofibrate	C10AB11
	cilostazol	B01AC23
	clevidipine	C08CA16
	collagenase clostridium histolyticum	M09AB02
	dienogest and estrogen	G03AB08

ATC level	INN/Common name	ATC code
	fingolimod	L04AA27
	flibanserin	G02CX02
	fluoroethylcholine (^{18}F)	V09IX08
	irbesartan and amlodipine	C09DB05
	lasofoxifene	G03XC03
	lisdexamfetamine	N06BA12
	naproxen and esomeprazole	M01AE52
	omacetaxine mepesuccinate	L01XX40
	pixantrone	L01DB11
	simvastatin, acetylsalicylic acid and ramipril	C10BX04
	ulipristal	G03AD02
	vandetanib	L01XE12
	velaglucerase alfa	A16AB10
	vernakalant	C01BG11

ATC code changes:

INN/common name	Previous ATC	New ATC
artemether and lumefantrine	P01BE52	P01BF0
levonorgestrel	G03AC03	G03AD01[1]
phentolamine	G04BE05	V03AB36

[1] *Oral products only indicated for emergency contraception*

ATC name changes

Previous	New	ATC code
Artemisinin and derivatives	Artemisinin and derivatives, plain	P01BE
influenza, purified antigen	influenza, inactivated, split virus or surface antigen	J07BB02[2]
Other class I antiarrhythmics	Other antiarrhythmics, class I and III	C01BG

[2] *This ATC 5th level name change will be implemented in the 2010 version of the ATC* index.

New DDDs:

INN/common name	DDD	Unit	Adm.R	ATC code
agomelatine	25	mg	O	N06AX22
basedoxifene	20	mg	O	G03CX02
ceftobiprole medocaril	1.5	g	P	J01DI01
choline fenofibrate	0.135	g[3]	O	C10AB11
eslicarbazepine	0.8	g	O	N03AF04

INN/common name	DDD	Unit	Adm.R	ATC code
golimumab	1.66	mg	P	L04AB06
liraglutide	1.2	mg	P	A10BX07
lisdexamfetamine	30	mg	O	N06BA12
milnacipran	0.1	g	O	N06AX17
olanzapine	10	mg	P depot	N05AH03
oxycodone, combinations	75	mg[4]	O	N02AA55
plerixafor	16.8	mg	P	L03AX16
saxagliptin	5	mg	O	A10BH03
silodosin	8	mg	O	G04CA04
tocilizumab	20	mg	P	L04AC07
ulipristal	30	mg	O	G03AD02

[3] refers to fenofibric acid
[4] refers to oxycodone

Change of DDDs

INN/common name	Previous DDD		New temporary DDD		ATC Code
Gliclazide	0.16g	O	60 mg	O	A10BB09
Nonacog alfa	1000 U	P	450 U	P	B02BD09

Consultation Document

The International Pharmacopoeia

Amoxicillin oral suspension

Draft proposal for *The International Pharmacopoeia* (June 2010). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Fax +41227914730 or e-mail to mendyc@who.int. A subscriber mailing list is now available to speed up consultation. For more information please contact bonnyw@who.int.

[Note from the Secretariat: This draft text is proposed for inclusion in The International Pharmacopoeia (Ph.Int.) in the context of collaboration between WHO and the Medicines and Healthcare products Regulatory Agency (MHRA) hosting The British Pharmacopoeia, on which this text is based.]

Category. Antibacterial.

Storage. The oral suspension should be stored in a tightly closed container at the temperature stated on the label and used within the period stated on the label.

The powder should be kept in a tightly closed container.

Labelling: The designation on the container of Amoxicillin oral suspension states that amoxicillin is in the trihydrate form and the quantity should be indicated in terms of equivalent amount of amoxicillin.

Additional information. Strengths in the current WHO Model List of Essential Medicines:125 mg per 5 ml (25 mg per ml), 250 mg per 5 ml (50 mg per ml).

Requirements

Complies with the monograph for “Liquid preparations for oral use”; the powder complies with the section of the monograph entitled “Powders for oral solutions, oral suspensions and oral drops”.

Definition Amoxicillin oral suspension is a suspension of Amoxicillin trihydrate in a suitable vehicle which may be flavoured. It is prepared from the powder as stated on the label just before issue for use. When freshly constituted, the oral suspension contains not less than 90.0% and not more than 120.0% of the amount of amoxicillin ($C_{16}H_{19}N_3O_5S$) stated on the label.

Manufacture. The product is formulated in such a way that when the suspension is constituted following manufacturer’s instructions, stored at the temperature and for the in-use period stated on the label and assayed using the method described below

under Assay, it contains not less than 80.0% of the amount of amoxicillin ($C_{16}H_{19}N_3O_5S$) stated on the label.

The manufacturing process and the product packaging are designed and controlled so as to minimize the moisture content of the powder. They ensure that, if tested, the powder would comply with a water limit of not more than 30 mg/g when determined as described under 2.8 Determination of water by the Karl Fischer method, Method A, using 0.5g of the powder.

Identity tests

A. Carry out the test as described under 1.14.1 Thin-layer chromatography, using a silica gel (Merck, silanised silica gel 60 F254s(RP-18) plates have been found suitable) as the coating substance and a mixture of 10 volumes of acetone R and 90 volumes of a solution of ammonium acetate (~154 g/l) TS adjusted to pH 5.0 with glacial acetic acid R as the mobile phase. Apply separately to the plate 1 μl of each of the following solutions. For solution (A), dilute a quantity of the oral suspension in sufficient sodium hydrogen carbonate solution (40 g/l) TS to produce a solution containing the equivalent of 2.5 mg of amoxicillin per ml. For solution (B) use 2.9 mg of amoxicillin trihydrate RS per ml of sodium hydrogen carbonate solution (42 g/l) TS. For solution (C) use 2.9 mg of amoxicillin trihydrate RS and 2.9 mg of ampicillin trihydrate RS per ml of sodium hydrogen carbonate solution (42 g/l) TS. After removal of the plate, allow it to dry in a current of air, expose it to iodine vapour until spots appear and examine in daylight.

The principal spot obtained with solution A corresponds in position, appearance, and intensity with that obtained with solution B. The test is not valid unless the chromatogram obtained with solution C shows two clearly separated spots.

B. See the test described below under Assay. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that of the principal peak in the chromatogram obtained with solution (2).

pH value (1.13). pH of the oral suspension, 4.0–7.0.

Assay

Use the oral suspension immediately after preparation. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with base deactivated particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (5 μm) (Waters, Spherisorb®, ODS1). As the mobile phase, use a mixture of 8 volumes of mobile phase B and 92 volumes of mobile phase A as described below.

Mobile phase A. Mix 1 volume of acetonitrile R and 99 volumes of a 250 g/l solution of potassium dihydrogen phosphate (27.2 g/l) TS adjusted to pH 5.0 with sodium hydroxide (2 mol/l) TS.

Mobile phase B. Mix 20 volumes of acetonitrile R and 80 volumes of a 250 g/l solution of potassium dihydrogen phosphate (27.2 g/l) adjusted to pH 5.0 with sodium hydroxide (~80g/l).

Prepare the following solutions. For solution (1) dilute an accurately weighed quantity of the oral suspension containing the equivalent of 60 mg of amoxicillin, with sufficient mobile phase A to produce 100 ml, mix and filter. For solution (2) use 0.70 mg of amoxicillin trihydrate RS per ml of mobile phase A. For solution (3) use 0.004 mg of cefadroxil R and 0.03 mg of amoxicillin trihydrate RS per ml of mobile phase A.

Operate with a flow rate of 1.0 ml per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of about 254 nm.

Inject separately 50 µl each of solution (1), (2) and (3).

The test is not valid unless, in the chromatogram obtained with solution (3), the resolution factor between the peaks due to amoxicillin and cefadroxil is at least 2.0. If necessary, adjust the composition of the mobile phase to achieve the required resolution.

Measure the areas of the peak responses obtained in the chromatograms from solution (1) and (2).

Determine the weight per ml (1.3.1) of the oral suspension and calculate the content of amoxicillin ($C_{16}H_{19}N_3O_5S$), weight in volume in the oral suspension using the declared content of amoxicillin trihydrate ($C_{16}H_{19}N_3O_5S,3H_2O$) in amoxicillin trihydrate RS. Each mg of $C_{16}H_{19}N_3O_5S,3H_2O$ is equivalent to 0.8711 mg of $C_{16}H_{19}N_3O_5S$.

*****

New reagent to be added in Ph.Int.

Cefadroxil. (6*R*,7*R*)-7-{[(2*R*)-2-amino-2-(4-hydroxyphenyl)acetyl]amino}-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. $C_{16}H_{17}N_3O_5S$.

A commercially available reagent of suitable grade.

Artesunate for injection

Draft proposal for *The International Pharmacopoeia* (June 2010). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Fax +41227914730 or e-mail to mendyc@who.int. A subscriber mailing list is now available to speed up consultation. For more information please contact bonnyw@who.int.

Category. Antimalarial.

Storage. Artesunate for injection should be kept in a hermetically closed container.

Additional information. Strength in the current WHO Model List of Essential Medicines: 60 mg.

Strength in the current WHO Model List of Essential Medicines for Children: 60 mg.

The reconstituted injection is a sterile solution of artesunate in 5% Sodium bicarbonate intravenous infusion. It is prepared by dissolving Artesunate for injection in the requisite amount of 5% Sodium bicarbonate intravenous infusion immediately before use. This solution is diluted further with a suitable diluent for injection in accordance with the manufacturer's instructions.

The reconstituted injection should be used immediately after preparation.

Requirements

The powder for injection and the reconstituted injection comply with the monograph for "Parenteral preparations".

Definition. Artesunate for injection is a sterile powder containing Artesunate. It contains not less than 90.0% and not more than 110.0% of the amount of artesunate ($C_{19}H_{28}O_8$) stated on the label.

Manufacture. The manufacturing process and the product packaging are designed and controlled so as to minimize the moisture content of the powder. They ensure that, if tested, the powder would comply with a water limit of not more than 5 mg/g when determined as described under 2.8 Determination of water by the Karl Fischer method, Method A.

Identity tests

Either test A alone or tests B, C, and D may be applied.

A. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from artesunate RS or with the *reference spectrum* of artesunate.

B. Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R5 as the coating substance and a mixture of 70 volumes of ethanol R, 30 volumes of toluene R and 1.5 volumes of ammonia (~260 g/l) TS as the mobile phase. Apply separately to the plate 1 µl of the following two solutions in methanol R. For solution (A) dissolve a quantity of the powder to obtain a solution containing 1.0 mg of Artesunate per ml. For solution (B) use 1.0 mg of artesunate RS per ml. After removing the plate from the chromatographic chamber, allow it to dry in air or in a current of cool air. Spray with anisaldehyde/methanol TS and heat the plate to 120 °C for 5 minutes. Examine the chromatogram in daylight.

The principal spot obtained with solution A corresponds in position, appearance, and intensity with that obtained with solution B.

C. Dissolve a quantity of the powder containing 0.1 g of Artesunate in 40 ml of dehydrated ethanol R, shake, and filter. To half of the filtrate (keep the remaining filtrate for test D) add about 0.5 ml of hydroxylamine hydrochloride TS2 and 0.25 ml of sodium hydroxide (~80 g/l) TS. Heat the mixture in a water-bath to boiling, cool, add 2 drops of hydrochloric acid (~70 g/l) TS and 2 drops of ferric chloride (50 g/l) TS; a light red-violet colour is produced.

D. Evaporate the remaining filtrate from test C on a water-bath to a volume of about 5 ml. Place a few drops of the mixture on a white porcelain dish, add one drop of vanillin/sulfuric acid TS1; a reddish-brown colour is produced.

Bacterial endotoxins. Carry out the test as described under 3.4 Test for bacterial endotoxins; contains not more than 2.5 IU of endotoxin per mg of artesunate.

Related substances

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given below under Assay method A.

Use solutions (1) and (3) as described under Assay method A. For solution (4) dilute woo1 ml of solution (1) to 100 ml with acetonitrile R.

Inject separately 20 μl each of solutions (1), (3) and (4). Record the chromatograms for about 4 times the retention time of artesunate. In the chromatogram obtained with solution (3), the following peaks are eluted at the following relative retention with reference to artesunate (retention time about 9 minutes): β-artenimol about 0.58, β-artenimol about 0.91 and impurity B (artemisinin) about 1.30. The test is not valid unless the peak-to-valley ratio (Hp/Hv) is at least 5.0, where Hp = height above the baseline of the peak due to -artenimol and Hv = the height above the baseline of the lowest point of the curve separating this peak from the peak due to artesunate. The chromatogram obtained with solution (1) may show a peak due to impurity C eluting at a relative retention of about 2.7 with reference to artesunate.

In the chromatogram obtained with solution (1):

– the combined areas of any peaks corresponding to α-artenimol and β-artenimol (impurity A) are not greater than the area of the principal peak obtained with solution (4) (1.0%);

– the area of any peak corresponding to impurity B (artemisinin) is not greater than 0.5 times the area of the principal peak obtained with solution (4) (0.5%);

– the area of any peak corresponding to impurity C, when multiplied by a correction factor of 0.07, is not greater than 0.3 times the area of the principal peak obtained with solution (4) (0.3%);

– the area of any other peak, other than the principal peak, is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (4) (0.3%);

– The sum of the corrected area of any peak corresponding to impurity C and the areas of all other peaks, other than the principal peak, is not greater than twice the area of the principal peak obtained with solution (4) (2.0%). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Assay

Either method A or method B may be applied.

A. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (10 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (3 μm) (Luna® has been found suitable). As the mobile phase, use a mixture of 44 volumes of acetonitrile R and 56 volumes of buffer pH 3.0.

Prepare the buffer pH 3.0 by dissolving 1.36 g of potassium dihydrogen phosphate R in 900 ml of water R, adjust the pH to 3.0 with phosphoric acid (~1440 g/l) TS and dilute to 1000 ml with water R.

Prepare the following solutions in acetonitrile R. For solution (1) determine the weight of the contents of 10 containers. Transfer a quantity of the mixed contents containing about 40 mg of Artesunate, accurately weighed, to a 10-ml volumetric flask, add 7 ml and shake to dissolve. Dilute to volume and filter. For solution (2) dissolve 40 mg of artesunate RS, accurately weighed, and dilute to 10 ml. For solution (3) dissolve about 1 mg of artenimol RS, about 1 mg of artemisinin RS and about 10 mg of artesunate RS in 10 ml.

Operate with a flow rate of 1.0 ml per minute. Maintain the column temperature at 30 °C and use as detector an ultraviolet spectrophotometer set at a wavelength of about 216 nm.

Inject separately 20 μl each of solutions (1), (2) and (3). Record the chromatograms for about 4 times the retention time of artesunate. In the chromatogram obtained with solution (3), the following peaks are eluted at the following relative retention with reference to artesunate (retention time about 9 minutes): α-artenimol about 0.58, β-artenimol about 0.91 and impurity B (artemisinin) about 1.30. The test is not valid unless the peak-to-valley ratio (Hp/Hv) is at least 5.0, where Hp = height above the baseline of the peak due to β-artenimol and Hv = the height above the baseline of the lowest point of the curve separating this peak from the peak due to artesunate. The chromatogram obtained with solution (1) may show a peak due to impurity C eluting at a relative retention of about 2.7 with reference to artesunate.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the content of artesunate ($C_{19}H_{28}O_8$) per sealed container.

B. Determine the weight of the contents of 10 containers. Dissolve a quantity of the mixed contents containing about 0.25 g of Artesunate, accurately weighed, in 25 ml of neutralized ethanol TS and titrate with sodium hydroxide (0.05 mol/l) VS, using 2 drops of phenolphthalein/ethanol TS as indicator.

Each ml of sodium hydroxide (0.05 mol/l) VS is equivalent to 19.22 mg of $C_{19}H_{28}O_8$. Calculate the content of artesunate per sealed container.

Impurities

The impurities limited by the requirements of this monograph include those listed in the monograph for Artesunate.

Didanosine capsules

Draft proposal for *The International Pharmacopoeia* (June 2010). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Fax +41227914730 or e-mail to mendyc@who.int. A subscriber mailing list is now available to speed up consultation. For more information please contact bonnyw@who.int.

Category. Antiretroviral (Nucleoside Reverse Transcriptase Inhibitor).

Storage. Didanosine capsules should be kept in a tightly closed container.

Additional information. Strengths in the current WHO Model list of essential medicines: 125 mg, 200 mg, 250 mg, 400 mg. Strengths in the current WHO Model list of essential medicines for children: 125 mg, 200 mg, 250 mg, 400 mg.
The capsules usually contain enteric-coated beadlets.

Requirements

Comply with the monograph for “Capsules”.

Definition. Didanosine capsules contain Didanosine. They contain not less than 90.0% and not more than 110.0% of the amount of didanosine ($C_{10}H_{12}N_4O_3$) stated on the label.

Identity tests

Either test A alone or tests B and C may be applied.

A. To a quantity of the contents of the capsules containing 50 mg of Didanosine add 10 ml of methanol R, shake to dissolve, and filter. Evaporate the filtrate to dryness. Carry out the examination with the residue as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from didanosine RS or with the *reference spectrum* of didanosine.

B. Carry out test B.1 or, where UV detection is not available, test B.2.

B.1. Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 67 volumes of dichloromethane R, 20 volumes of acetonitrile R, 10 volumes of methanol R and 3 volumes of ammonia (~ 260 g/l) TS as the mobile phase. Apply separately to the plate 5 μl of each of the following 2 solutions in methanol R. For solution (A) shake a quantity of the contents of the capsules containing 25 mg of Didanosine with 5 ml, filter and use the

clear filtrate. For solution (B) use 5 mg of didanosine RS per ml. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or in a current of cool air. Examine the chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution A corresponds in position, appearance and intensity to that obtained with solution B.

B.2. Carry out the test as described under 1.14.1 Thin-layer chromatography, using the conditions described above under test A.1 but using silica gel R5 as the coating substance. Spray with vanillin/sulfuric acid TS1. Heat the plate for a few minutes at 120 °C. Examine the chromatogram in daylight.

The principal spot obtained with solution A corresponds in position, appearance and intensity to that obtained with solution B.

C. To a quantity of the contents of the capsules containing 20 mg of Didanosine add 100 ml of methanol R, shake and filter. Dilute 5 ml of the filtrate to 100 ml with the same solvent. The absorption spectrum (1.6) of the resulting solution, when observed between 210 nm and 300 nm, exhibits one maximum at about 250 nm.

Disintegration

[Note from Secretariat: the possibility of including a disintegration test for enteric-coated dosage forms is under investigation.]

Related substances
Prepare fresh solutions and perform the tests without delay.

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm), packed with octadecylsilyl base-deactivated silica gel for chromatography R (5 μm).

The mobile phases for gradient elution consist of a mixture of Mobile phase A and Mobile phase B, using the following conditions:

Mobile phase A: 0.05 M solution of ammonium acetate R adjusted to pH 8.0 using ammonia (~ 100g/l) TS.

Mobile phase B: methanol R.

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0 – 18	92	8	Isocratic
18 – 25	92 to 70	8 to 30	Linear gradient
25 – 45	70	30	Isocratic
45 – 50	70 to 92	30 to 8	Return to initial composition
50 – 60	92	8	Re-equilibration

Prepare the following solutions in a mixture of 92 volumes of mobile phase A and 8 volumes of mobile phase B (dissolution solvent).

For solution (1) transfer a quantity of the contents of the capsules containing 25 mg of Didanosine into a 50–ml volumetric flask. Add about 20 ml of the dissolution solvent, sonicate for about 15 minutes and make up to volume using the dissolution solvent. Filter a portion of this solution through a 0.45-μm filter, discarding the first few ml of the filtrate. For solution (2) dissolve 5 mg of didanosine for system suitability RS (containing impurities A to F) in the dissolution solvent and dilute to 10 ml with the same solvent. For solution (3) dissolve 5.0 mg of hypoxanthine R in the dissolution solvent and dilute to 100.0 ml with the same solvent. Dilute 1.0 ml of this solution to 20.0 ml with the same solvent. For solution (4) dilute 5.0 ml of solution (1) to 50.0 ml with the dissolution solvent; dilute 5.0 ml of this solution to 50.0 ml with the same solvent.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 254 nm.

Use the chromatogram supplied with didanosine for system suitability RS and the chromatogram obtained with solution (2) to identify the peaks due to impurities A to F.

Inject 20 μl of solution (2). The test is not valid unless the resolution factor between the peaks due to impurity C (2'-deoxyinosine) and impurity D (3'-deoxyinosine) is at least 2.5; if necessary reduce the amount of methanol in the mobile phase and adjust the proportion of aqueous phase pH 8.0 accordingly.

Inject separately 20 μl each of solutions (1), (3) and (4) and of the mobile phase in the chromatographic system. Examine the mobile phase chromatogram for any extraneous peaks and disregard the corresponding peaks observed in the chromatogram obtained with solution (1).

In the chromatogram obtained with solution (2), the following peaks are eluted at the following relative retention times with reference to didanosine (retention time about 13–15 minutes): impurity A about 0.3; impurity B about 0.4; impurity C about 0.44; impurity D about 0.48; impurity E about 0.5; impurity F about 0.8; impurity I about 1.4; impurity G about 1.6; impurity H about 2.0.

In the chromatogram obtained with solution (1) the area of any peak corresponding to impurity A (hypoxanthine) is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.5%). The area of any individual peak corresponding to impurities B, C, D, E, F or G is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (4) (0.2%). The area of any other impurity peak is not greater than 0.1 times the area of the principal peak in the chromatogram obtained with solution (4) (0.1%). The sum of the areas of all peaks, other than the principal peak, is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (1.0%). Disregard any peak with an area less than 0.05 times the area of the principal peak in the chromatogram obtained with solution (4) (0.05%).

Assay

Either method A or method B may be applied.

A. Carry out the test under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with base deactivated particles of silica gel the surface of which has been modified with chemically bonded octadecylsilyl groups (5 μm) (Hypersil® BDS has been found suitable).

As the mobile phase use a solution prepared as follows: 90 volumes of a 0.05 M solution of ammonium acetate R adjusted to pH 8.0 using ammonia (~100 g/l) TS and 10 volumes of methanol R.

Prepare the following solutions using the mobile phase as diluent. For solution (1) weigh and mix the contents of 20 capsules and transfer a quantity containing about 0.025 g of Didanosine, accurately weighed, into a 50-ml volumetric flask. Add about 40 ml of mobile phase, sonicate for about 5 minutes, allow to cool to room temperature, and make up to volume using the same solvent. Filter a portion of this solution through a 0.45-μm filter, discarding the first few ml of the filtrate. Dilute 1.0 ml of that solution to 100.0 ml with the mobile phase. For solution (2) use 0.005 mg of didanosine RS per ml of mobile phase.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 254 nm.

Inject separately 20 μl each of solutions (1) and (2) and record the chromatograms for 1.5 times the retention time of didanosine.

Measure the areas of the peak responses obtained in the chromatograms from solution (1) and (2), and calculate the content of didanosine ($C_{10}H_{12}N_4O_3$) in the capsules.

B. Weigh and mix the contents of 20 capsules and transfer a quantity containing about 25 mg of Didanosine, accurately weighed, to a 50-ml volumetric flask. Add about 25 ml of methanol R, sonicate for about 5 minutes, allow to cool to room temperature, and make up to volume using the same solvent. Filter a portion of this solution through a 0.45-μm filter, discarding the first few ml of the filtrate. Dilute 1.0 ml of the filtrate to 50.0 ml with the same solvent. Measure the absorbance (1.6) of this solution in a 1-cm layer at the maximum at about 250 nm against a solvent cell containing methanol R.

Calculate the content of didanosine ($C_{10}H_{12}N_4O_3$) in the capsules using an absorptivity value of 45 ($A^{1\%}_{1\ cm} = 450$).

Impurities. The impurities limited by the requirements of this monograph include those listed in the monograph for Didanosine.

Efavirenz tablets

Draft proposal for *The International Pharmacopoeia* (June 2010). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Fax +41227914730 or e-mail to mendyc@who.int. A subscriber mailing list is now available to speed up consultation. For more information please contact bonnyw@who.int.

Category. Antiretroviral (Non-nucleoside Reverse Transcriptase Inhibitor).

Storage. Efavirenz tablets should be kept in a well-closed container, protected from light.

Additional information. Strengths in the current WHO Model List of Essential Medicines: 600 mg. Strengths in the current WHO Model List of Essential Medicines for Children: 600 mg.

Requirements

Comply with the monograph for "Tablets".

Definition. Efavirenz tablets contain Efavirenz. They contain not less than 90.0% and not more than 110.0% of the amount of Efavirenz ($C_{14}H_9ClF_3NO_2$) stated on the label.

Identity tests

Either test A alone or tests B and D or tests C and D may be applied.

A. To a quantity of the powdered tablets containing 25 mg of Efavirenz, add 10 ml of methanol R, shake to dissolve and filter. Evaporate the filtrate to dryness. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from efavirenz RS or with the reference spectrum of efavirenz.

If the spectra thus obtained are not concordant, repeat the test using the test residue and the residue obtained by dissolving efavirenz RS in a small amount of methanol R and evaporating to dryness. The infrared absorption spectrum is concordant with the spectrum obtained from efavirenz RS.

B. Carry out test B.1 or, where UV detection is not available, test B.2.

B.1. Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 90 volumes of dichloromethane R, 10 volumes of methanol R and 3 volumes of glacial acetic acid R as the mobile phase. Apply separately to the plate 5 μl of each of the following two solutions in methanol R. For solution (A) shake a quantity of the powdered tablets containing 5 mg of Efavirenz with 5 ml, filter and use the clear filtrate. For solution (B) use 1 mg of efavirenz RS per ml. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or in a current of cool air. Examine the chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution A corresponds in position, appearance and intensity with that obtained with solution B.

B.2. Carry out the test as described under 1.14.1 Thin-layer chromatography, using the conditions described under test A.1 but using silica gel R5 as the coating substance. Spray the plate with basic potassium permanganate (~1 g/l) TS. Examine the chromatogram in daylight.

The principal spot obtained with solution A corresponds in position, appearance and intensity with that obtained with solution B.

C. See the test described under Assay method A. The retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that in the chromatogram obtained with solution (2).

D. The absorption spectrum of the final solution prepared for Assay method B, when observed between 210 nm and 300 nm, exhibits one maximum at about 247 nm.

Related substances. Prepare fresh solutions and perform the test without delay.

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given under Assay Method A.

Prepare the following solutions in the dissolution solvent, a mixture of equal volumes of acetonitrile R and water R.

For solution (1) transfer a quantity of the powdered tablets containing about 25 mg of Efavirenz into about 20 ml of the dissolution solvent, sonicate for 5 minutes, allow to cool to room temperature and dilute to 25.0 ml with the same solvent. Filter a portion of this solution through a 0.45-μm filter, discarding the first few ml of the filtrate. For solution (2) dilute 1.0 ml of solution (1) to 50.0 ml with the dissolution solvent and dilute 5.0 ml of the resulting solution to 100.0 ml with the same solvent. For solution (3) dissolve about 5 mg of efavirenz RS in 5 ml of a solution prepared as follows: dissolve 1 mg of efavirenz impurity B RS in the dissolution solvent and dilute to 10 ml with the same solvent. Dilute 1 ml of the resulting solution to 25 ml with the dissolution solvent.

Inject separately 35 μl each of solutions (1), (2) and (3) and of the dissolution solvent in the chromatographic system. Examine the blank chromatogram for any extraneous peaks and disregard the corresponding peaks observed in the chromatogram obtained with solution (1).

In the chromatogram obtained with solution (3), the peak due to impurity B is eluted at a relative retention of about 0.9 with reference to efavirenz (retention time about 20 minutes). The test is not valid unless the resolution factor between the peaks due to impurity B and efavirenz is at least 3.

In the chromatogram obtained with solution (1) the area of any peak corresponding to impurity B is not greater than four times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%), the area of any other peak, apart from the principal peak, is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%) and the area of not more than three such peaks

is greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%). The sum of the areas of all peaks, other than the principal peak, is not greater than eight times the area of the principal peak in the chromatogram obtained with solution (2) (0.8%). Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Assay

Either method A or method B may be applied.

A Carry out the assay as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (15 cm x 4.6 mm), packed with cyanopropyldimethylsilane monolayer (3.5 μm) (Zorbax® SB-CN has been found to be suitable).

The mobile phases for gradient elution consist of a mixture of Mobile phase A and Mobile phase B, using the following conditions:

Mobile phase A: 90 volumes of a 0.05% solution of trifluoroacetic acid R and 10 volumes of methanol R.

Mobile phase B: 10 volumes of a 0.05% solution of trifluoroacetic acid R and 90 volumes of methanol R.

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0 – 16	60 to 50	40 to 50	Linear gradient
16 – 23	50 to 35	50 to 65	Linear gradient
23 – 28	35 to 30	65 to 70	Linear gradient
28 – 29	30 to 20	70 to 80	Linear gradient
29 – 31	20	80	Isocratic
31 – 32	20 to 60	80 to 40	Return to initial composition
32 – 40	60	40	Re-equilibration

Prepare the following solutions in the dissolution solvent, a mixture of equal volumes of acetonitrile R and water R

For solution (1) weigh and powder 20 tablets. Transfer a quantity of the powdered tablets containing about 25 mg of Efavirenz, accurately weighed, into about 20 ml of the dissolution solvent, sonicate for 5 minutes, allow to cool to room temperature and dilute to 25.0 ml with the same solvent. Filter a portion of this solution through a 0.45-μm filter, discarding the first few ml of the filtrate. Dilute 1.0 ml of the resulting solution to 100.0 ml with the dissolution solvent. For solution (2) dissolve 25 mg of efavirenz RS in the dissolution solvent and dilute to 25.0 ml with the same solvent. Dilute 1.0 ml of the resulting solution to 100.0 ml with the dissolution solvent. For solution (3) dissolve about 5 mg of efavirenz RS in 5 ml of a solution prepared as follows: dissolve 1 mg of efavirenz impurity B RS in the dissolution solvent and dilute to 10 ml with the same solvent. Dilute 1 ml of the resulting solution to 25 ml with the dissolution solvent.

Operate with a flow rate of 1.5 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 250 nm.

Inject separately 35 µl each of solutions (1), (2) and (3). In the chromatogram obtained with solution (3), the peak due to impurity B is eluted at a relative retention of about 0.9 with reference to efavirenz (retention time about 20 minutes). The assay is not valid unless the resolution factor between the peaks due to impurity B and efavirenz is at least 3.

Measure the areas of the peaks responses obtained in the chromatograms from solutions (1) and (2), and calculate the content of efavirenz ($C_{14}H_9ClF_3NO_2$) in the tablets.

B. Weigh and powder 20 tablets. Transfer a quantity of the powdered tablets containing about 25 mg of Efavirenz, accurately weighed, to a 50-ml volumetric flask. Add about 25 ml of methanol R, sonicate for about 5 minutes, allow to cool to room temperature and make up to volume using the same solvent. Filter a portion of this solution through a 0.45-µm filter, discarding the first few ml of the filtrate. Dilute 1.0 ml of this solution to 50.0 ml with methanol R. Measure the absorbance (1.6) of a 1-cm layer of this solution at the maximum at about 247 nm. Calculate the content of efavirenz ($C_{14}H_9ClF_3NO_2$) in the tablets using an absorptivity value of 55.0

($A\ ^{1\%}_{1\ cm} = 550$).

Impurities. The impurities limited by the requirements of this monograph include those listed in the monograph for Efavirenz.

Mefloquine tablets

Draft proposal for *The International Pharmacopoeia* (June 2010). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Fax +41227914730 or e-mail to mendyc@who.int. A subscriber mailing list is now available to speed up consultation. For more information please contact bonnyw@who.int.

Category. Antimalarial.

Storage. Mefloquine tablets should be kept in a well-closed container, protected from light.

Labelling. The designation of the container of Mefloquine tablets should state that the active ingredient is in the hydrochloride form and the quantity should be indicated in terms of the equivalent amount of mefloquine.

Additional information. Strength in the current WHO Model List of Essential Medicines: 250 mg. Strength in the current WHO Model List of Essential Medicines for Children: 250 mg.

Requirements

Comply with the monograph for "Tablets".

Definition. Mefloquine tablets contain Mefloquine hydrochloride. They contain not less than 90.0% and not more than 110.0% of the amount of mefloquine ($C_{17}H_{16}F_6N_2O$) stated on the label.

Identity tests

Any two of tests A, B or C may be applied together with test D.

A. Carry out test A.1 or, where UV detection is not available, test A.2.

A.1. Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 70 volumes of toluene R, 30 volumes of ethanol R and 2 volumes of 25% ammonia solution R as the mobile phase. Apply separately to the plate 10 µl of each of the following two solutions in methanol R. For solution (A) sonicate, with intermittent shaking, a quantity of the powdered tablets containing the equivalent of about 250 mg of mefloquine for 5 minutes with 25 ml, filter, and use the filtrate. For solution (B) use 10 mg of mefloquine RS per ml. After removing the plate from the chromatographic chamber, allow it to dry in a current of air and examine the chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution A corresponds in position, appearance and intensity to that obtained with solution B.

A.2 Carry out the test as described under 1.14.1 Thin-layer chromatography, using the conditions described above under test A.1 but using silica gel R5 as the coating substance. Stain the plate with iodine vapours. Examine the chromatogram in daylight.

The principal spot obtained with solution A corresponds in position, appearance, and intensity to that obtained with solution B.

B. See the test described under Assay. The retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that in the chromatogram obtained with solution (2).

C. To a quantity of the powdered tablets containing the equivalent of 50 mg of mefloquine add 100 ml of methanol R, shake and filter. Dilute 5 ml of the filtrate to 50 ml with the same solvent. The absorption spectrum (1.6) of the resulting solution, when observed between 250 nm and 290 nm, exhibits one maximum at about 283 nm.

D To a quantity of powdered tablets containing the equivalent of about 0.5 g of mefloquine add 10 ml of water R, sonicate for 10 minutes and filter. The filtrate yields reaction B described under 2.1 General identification tests as characteristic of chlorides.

Dissolution

Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms, using as the dissolution medium, 900 ml of 0.1 mol/l hydrochloric acid and rotating the

paddle at 75 revolutions per minute. At 30 minutes withdraw a sample of 10 ml of the medium through an in-line filter. Measure the absorbance (1.6) of a 1-cm layer of the filtered sample, suitably diluted if necessary, at the maximum at about 283 nm. At the same time measure the absorbance at the maximum at about 283 nm of a suitable solution of mefloquine hydrochloride RS, initially dissolved in methanol R and then diluted in 0.1 mol/l hydrochloric acid, using 0.1 mol/l hydrochloric acid as the blank. Each mg of mefloquine hydrochloride ($C_{17}H_{16}F_6N_2O,HCl$) is equivalent to 0.912 mg of mefloquine ($C_{17}H_{16}F_6N_2O$).

For each of the six tablets tested, calculate the total amount of mefloquine ($C_{17}H_{16}F_6N_2O$) in the medium. The amount in solution for each tablet is not less than 80% of the amount declared on the label. If the amount obtained for one of the six tablets is less than 80%, repeat the test using a further six tablets; the average amount for all 12 tablets tested is not less than 75% and the amount obtained for no tablet is less than 60%.

Related substances

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions described under Assay.

Use solutions (1) and (4) as described under Assay. For solution (5) transfer 1 ml of solution (1) as prepared for the assay, to a 50-ml volumetric flask and make up to volume with the mobile phase. Dilute 2 ml of this solution to 20 ml with the mobile phase.

Inject 20 μl of solution (4). The test is not valid unless the resolution between the two principal peaks is at least 5.

Inject separately 20 μl each of solutions (1) and (5). Record the chromatograms for about 10 times the retention time of mefloquine.

In the chromatogram obtained with solution (1) the following impurities, if present, are eluted at the following relative retention with reference to mefloquine (retention time about 3.9 minutes): impurity A about 0.9, impurity C about 3.6 and impurity B about 7.4.

In the chromatogram obtained with solution (1) the area of any peak, other than the peak due to mefloquine, is not greater than the area of the principal peak in the chromatogram obtained with solution (5) (0.2%). The sum of the areas of all peaks, other than the peak due to mefloquine, is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (5) (0.5%). Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

[Note from Secretariat. The limit of 0.2% for individual related substances in this test is tighter than the limit of 0.5% in the current International Pharmacopoeia monograph for mefloquine hydrochloride API, as determined by TLC. It is therefore intended to revise accordingly the related substances test of the API monograph (list of impurities, limits).]

Assay

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (5 μm) (Luna® was found suitable).

As the mobile phase, use a mixture of 22 volumes of methanol R, 38 volumes of acetonitrile R and 40 volumes of buffer pH 3.5 prepared as follows: dissolve 13.6 g potassium dihydrogen phosphate in about 900 ml of water R, adjust the pH to 3.5 by addition of 10% phosphoric acid and dilute to 1000 ml.

Prepare the following solutions in mobile phase. For solution (1), weigh and powder 20 tablets. Transfer a quantity of the powder containing the equivalent of about 200 mg of mefloquine, accurately weighed, into a 100-ml volumetric flask. Add 70 ml of mobile phase and sonicate for about 10 minutes. Allow to cool to room temperature and make up to volume with mobile phase. Filter a portion of this solution through a 0.45-μm filter, discarding the first few ml of the filtrate. For solution (2) dilute 5 ml of solution (1) to 50 ml with mobile phase. For solution (3), use 0.22 mg of mefloquine hydrochloride RS per ml. For solution (4) use about 0.22 mg of mefloquine hydrochloride RS and about 0.04 mg of sulfadoxine R per ml.

Operate with a flow rate of 1.5 ml per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of about 283 nm.

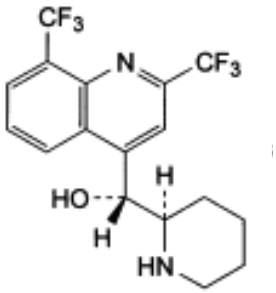
Inject 20 μl of solution (4). The assay is not valid unless the resolution between the two principal peaks is at least 5.

Inject separately 20 μl each of solutions (2) and (3).

Measure the areas of the peaks responses obtained in the chromatograms from solutions (2) and (3) and calculate the content of mefloquine ($C_{17}H_{16}F_6N_2O$) in the tablets, using the declared content of mefloquine hydrochloride ($C_{17}H_{16}F_6N_2O$,HCl) in mefloquine hydrochloride RS. Each mg of mefloquine hydrochloride ($C_{17}H_{16}F_6N_2O$,HCl) is equivalent to 0.912 mg of mefloquine ($C_{17}H_{16}F_6N_2O$).

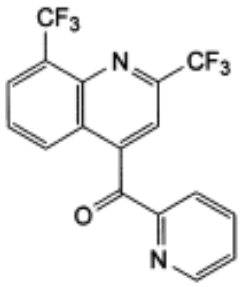
Impurities

The following list of known and potential impurities that have been shown to be controlled by the tests in this monograph is given for information.



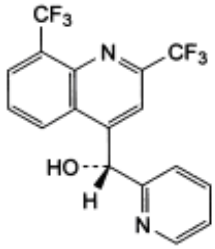
and enantiomer

A.(*RS*)-[2,8-bis(trifluoromethyl)quinolin-4-yl][(2*RS*)-piperidin-2-yl]methanol *(threo*-mefloquine)



and enantiomer

B.(*RS*)-[2,8-bis(trifluoromethyl)quinolin-4-yl](pyridin-2-yl]methanone



C.(*RS*)-[2,8-bis(trifluoromethyl)quinolin-4-yl](pyridin-2-yl]methanol

*****

New reagent to be added to International Parmacopoeia

Sulfadoxine R. *N*[1]-(5,6-Dimethoxy-4-pyrimidinyl)sulfanilamide; 4-amino-*N*-(5,6-dimethoxy-4-pyrimidinyl)benzenesulfonamide; $C_{12}H_{14}N_4O_4S$

A commercialy available reagent of suitable grade.

Description. A white or creamy white, crystalline powder.

Solubility: Very slightly soluble in water; slightly soluble in ethanol (~750 g/l) TS and in methanol R; practically insoluble in ether R.

Metronidazole oral suspension

Draft proposal for *The International Pharmacopoeia* (June 2010). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Fax +41227914730 or e-mail to mendyc@who.int. A subscriber mailing list is now available to speed up consultation. For more information please contact bonnyw@who.int.

[Note from the Secretariat: This draft text is proposed for inclusion in The International Pharmacopoeia in the context of collaboration between WHO and the Medicines and Healthcare Products Regulatory Agency (MHRA) hosting The British Pharmacopoeia, on which this text is based.]

Category. Antibacterial.

Storage. Metronidazole oral suspension should be kept in a well-closed container, protected from light.

Labelling. The designation of the container of Metronidazole oral suspension should state that the active ingredient is in the benzoate form and the quantity should be indicated in terms of equivalent amount of metronidazole.

Additional information. Strengths in the current WHO Model List of Essential Medicines: 200 mg per 5 ml (40 mg per ml).

Requirements

Complies with the monograph for "Liquid preparations for oral use".

Definition. Metronidazole oral suspension is a suspension of Metronidazole benzoate in a suitable vehicle which may be flavoured. It contains not less than 90.0% and not more than 110.0% of the amount of metronidazole ($C_6H_9N_3O_3$) stated on the label.

[Note from the Secretariat: wider limits than those stated in the British Pharmacopoeia monograph (95.0%–105.0%) are proposed, to be in line with the policy and limits applied for similar dosage forms in The International Pharmacopoeia.]

Identity tests

Either test A or any two of tests B, C and D may be applied.

A. To a quantity of the oral suspension containing the equivalent of 200 mg of Metronidazole add 20 ml of water R, filter under partial vacuum and wash the residue with three quantities of 10 ml of water R. Dissolve the residue as completely as possible in 10 ml of acetone R, filter and evaporate the filtrate to dryness. Dry the residue at 60 °C and carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from metronidazole benzoate RS or with the *reference spectrum* of metronidazole benzoate.

B. Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R6 as the coating substance. Heat to activate the plate at 110°C for 1 hour and cool before use. As the mobile phase, use ethyl acetate R. Apply separately to the plate 10 l of each of the following two solutions. For solution (A), shake and dilute a quantity of the oral suspension containing 200 mg of Metronidazole benzoate to 100 ml with acetone R, filter, and use the filtrate. For solution (B), use 2.0 mg of metronidazole benzoate RS per ml of acetone R. After removing the plate from the chromatographic chamber, allow it to dry in a current of air, and examine the chromatogram in ultraviolet light (254 nm). For solution (C) dissolve 20 mg of metronidazole RS in 10 ml of solution (B).

The principal spot obtained with solution A corresponds in position, appearance, and intensity with that obtained with solution B. The test is not valid unless the chromatogram obtained with solution (C) shows two clearly separated spots.

C. Dilute a quantity of the oral suspension containing 100 mg of Metronidazole benzoate to 100 ml with a 103 g/l solution of hydrochloride acid R, filter, and further dilute 1 ml of the filtrate to 100 ml with the same solvent. The absorption spectrum (1.6) of this solution, when observed between 220 nm and 350 nm, exhibits two absorption maxima at 232 nm and 275 nm.

D. See the test described below under Assay. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that of the principal peak in the chromatogram obtained with solution (2).

pH value. (1.13) pH of the oral suspension, 5.0–6.5.

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given below under Assay.

Prepare the following solutions. For solution (1), to a quantity of the oral suspension containing the equivalent of 200 mg of Metronidazole, add 150 ml of methanol R and sufficient water R, with mixing and cooling, to produce 250 ml, shake and centrifuge. For solution (2), dissolve 20 mg of metronidazole RS in 150 ml of methanol R and add sufficient water R, with mixing and cooling, to produce 250 ml. Dilute 1 volume to 10 volumes with a 60% solution of methanol R.

Inject separately 30 μl each of solution (1) and (2).

In the chromatogram obtained with solution (1), the area of any peak corresponding to metronidazole, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%).

Assay

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with base deactivated particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilanes groups (5 μm) (Hypersil® BDS C18 has been found suitable). As the mobile phase, use a mixture of 40 volumes of a 12.5 g/l solution of ammonium acetate R, adjusted to pH 7.0 with ammonia (~100 g/l) TS and 60 volumes of methanol R.

Prepare the following solutions. For solution (1), to a quantity of the oral suspension containing the equivalent of 200 mg of Metronidazole, add 150 ml of methanol R and sufficient water R, with mixing and cooling, to produce 250 ml. Shake and centrifuge. Dilute 10 ml of the resulting solution to 100 ml with a 60% solution of methanol R. For solution (2), dissolve 64 mg of metronidazole benzoate RS in 1 ml of dimethylformamide R and 30 ml of methanol R and add sufficient water R, with mixing and cooling, to produce 50 ml. Dilute 10 ml of the resulting solution to 100 ml with a 60% solution of methanol R.

Operate with a flow rate of 1.0 ml per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of about 310 nm.

Inject separately 30 μl each of solution (1) and (2).

Measure the areas of the peak responses obtained in the chromatograms from solution (1) and (2).

Determine the weight per ml (1.3.1) of the oral suspension and calculate the content of metronidazole ($C_6H_9N_3O_3$), weight in volume, in the oral suspension using the declared content of metronidazole benzoate ($C_{13}H_{13}N_3O_4$) in metronidazole benzoate RS. Each mg of $C_{13}H_{13}N_3O_4$ is equivalent to 0.6219 mg of $C_6H_9N_3O_3$.

Oseltamivir capsules

Draft proposal for *The International Pharmacopoeia* (June 2010). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Fax +41227914730 or e-mail to mendyc@who.int. A subscriber mailing list is now available to speed up consultation. For more information please contact bonnyw@who.int.

Category. Antiviral.

Storage. Oseltamivir capsules should be kept in a well closed container, protected from light.

Labelling. The designation of the container of Oseltamivir capsules should state that the active ingredient is in the sulfate form and the quantity should be indicated in terms of equivalent amount of oseltamivir.

Additional information. Strengths in the current WHO Model list of essential medicines: 30 mg, 45 mg, 75 mg. Strengths in the current WHO Model list of essential medicines for children: 30 mg, 45 mg, 75 mg.

1 mg of oseltamivir is equivalent to approximately 1.3 mg of oseltamivir sulfate.

Requirements

Comply with the monograph for “Capsules”.

Definition. Oseltamivir capsules contain Oseltamivir phosphate. They contain not less than 90.0% and not more than 110.0% of the amount of Oseltamivir ($C_{16}H_{28}N_2O_4$) stated on the label.

Identity tests

Either tests A, C and D or tests B and D may be applied

A. Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 8 volumes of methanol R, 6 volumes of ethyl acetate R, 4 volumes of toluene R and 2 volumes of ammonia (~260g/l) TS as the mobile phase. Apply separately to the plate 10 µl of each of the following two solutions in methanol R. For solution (A) shake a quantity of the contents of the capsules containing 10 mg of Oseltamivir phosphate with 5 ml, filter and

use the clear filtrate. For solution (B) use 2 mg of oseltamivir phosphate RS per ml. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or in a current of cool air. Examine the chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution A corresponds in position, appearance, and intensity to that obtained with solution B.

B. To a quantity of the contents of the capsules containing 25 mg of Oseltamivir phosphate, add 10 ml of methanol R, shake to dissolve and filter. Evaporate the filtrate to dryness.

Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from oseltamivir phosphate RS or with the *reference spectrum* of oseltamivir phosphate.

C. See the test described under Assay method A. The retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that in the chromatogram obtained with solution (2).

D. Dissolve a quantity of the contents of the capsules to obtain a solution containing 4 mg per ml. Neutralize this solution with a few ml of sodium hydroxide (0.1 mol/l) VS. Use 5 ml of the resulting solution; it yields reaction B described under 2.1 General identification tests as characteristic of orthophosphates.

Related substances. Carry out the test as described under 1.14.4 High performance liquid chromatography, using the same conditions as under Assay, method A using solutions (1), (3) and (4).

Inject separately 15 µl each of solutions (1), (3) and (4) and of the dissolution solvent in the chromatographic system. Examine the blank chromatogram for any extraneous peaks and disregard the corresponding peaks observed in the chromatogram obtained with solution (1).

Use the chromatogram obtained with solution (4) to identify the peaks due to impurities A, B, C and D. The impurity peaks are eluted at the following relative retention with reference to oseltamivir phosphate (retention time about 19 minutes): impurity A about 0.16, impurity B about 0.17, impurity C about 0.51, impurity D about 0.55 and impurity F about 1.5. The test is not valid unless the resolution between the peaks due to impurities A and B and that between the peaks due to impurities C and D is at least 1.3.

In the chromatogram obtained with solution (1) the area of any peak corresponding to impurity B, when multiplied by a correction factor of 1.4, is not greater than 20 times the area of the peak in the chromatogram obtained with solution (3) (2.0%), the area of any peak corresponding to impurity C, when multiplied by a correction factor of 0.6, is not greater than 3 times the area of the peak in the chromatogram obtained with solution (3) (0.3%), the area of any peak corresponding to impurity F is not greater than 5 times the area of the peak in the chromatogram obtained with solution (3)

(0.5%), the area of any other peak, apart from the principal peak, is not greater than the area of the peak in the chromatogram obtained with solution (3) (0.1%). The sum of the corrected areas of any peaks corresponding to impurities B or C and of the areas of all other peaks, apart from the principal peak, is not greater than 30 times the area of the peak obtained with solution (3) (3.0%). Disregard any peak with an area less than 0.5 times the area of the principal peak obtained with solution (3) (0.05%).

Assay

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with octylsilyl silica gel for chromatography (5 μm) (Waters Symmetry C8 is suitable).

The mobile phase consists of a mixture of 620 volumes of 0.05 M potassium dihydrogen phosphate (adjusted to pH 6 with potassium hydroxide (~110g/l TS), 245 volumes of methanol R and 135 volumes of acetonitrile R.

Operate with a flow rate of 1.2 ml per minute and the column oven temperature at 50 °C. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 207 nm.

Prepare the following solutions in a mixture of 620 volumes of water R, 245 volumes of methanol R and 135 volumes of acetonitrile R (dissolution solvent).

For solution (1) weigh and mix the contents of 20 capsules and transfer a quantity containing 40 mg of oseltamivir into a 50-ml volumetric flask. Add about 20 ml of the dissolution solvent, sonicate for about 15 minutes and make up to volume using the dissolution solvent. Filter a portion of this solution through a 0.45 μm filter, discarding the first few ml of the filtrate. For solution (2) dissolve 50 mg of oseltamivir phosphate RS in the dissolution solvent and dilute to 50.0 ml with the same solvent. For solution (3) dilute 1.0 ml of solution (1) to 100 ml with the dissolution solvent and then dilute 1.0 ml of this solution to 10 ml with the same solvent. For solution (4) dissolve about 2 mg of oseltamivir for system suitability RS in the dissolution solvent and dilute to 2 ml with the same solvent.

Inject separately 15μ l each of solutions (1), (2) and (4) and of the dissolution solvent in the chromatographic system. The assay is not valid unless, in the chromatogram obtained with solution (4), the resolution between the peaks due to impurities A and B and that between the peaks due to impurities C, and D is at least 1.3.

Measure the areas of the peak responses in the chromatograms obtained with solutions (1) and (2). Calculate the content of oseltamivir ($C_{16}H_{28}N_2O_4$).

Impurities. The impurities limited by the requirements of this monograph include those listed in the monograph for Oseltamivir phosphate.

Sodium bicarbonate intravenous infusion

Draft proposal for *The International Pharmacopoeia* (June 2010). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Fax +41227914730 or e-mail to mendyc@who.int. A subscriber mailing list is now available to speed up consultation. For more information please contact bonnyw@who.int.

Category. Alkalinizing agent.

Storage. Sodium bicarbonate intravenous infusion should be kept in a sealed container. Containers that have previously been subjected to heating in an autoclave should not be re-used to keep Sodium bicarbonate intravenous infusion.

Labelling. The designation on the container of Sodium bicarbonate intravenous infusion should state:

- the strength as the percentage m/v of Sodium bicarbonate, as well as the approximate concentrations, in millimoles per litre, of the sodium ions and the bicarbonate ions;
- that containers containing visible particles due to the possible formation of sodium carbonate precipitates must not be used.

Additional information. For a preparation containing 1% m/v of Sodium bicarbonate the concentration of each ion is about 119 millimoles per litre.

Requirements

Complies with the monograph for “Parenteral Preparations”.

Definition. Sodium bicarbonate intravenous infusion is a sterile solution of Sodium bicarbonate in Water for injections. It contains not less than 94.0% and not more than 106.0% of the amount of sodium bicarbonate ($NaHCO_3$) stated on the label.
The infusion is sterilized by a suitable method (see 5.8 Methods of sterilization).

Identity tests

A. The infusion yields reaction A described under 2.1 General identification tests, as characteristic of sodium.

B. Introduce 2 ml of the infusion into a test tube and add 3 ml of acetic acid (~120 g/l) TS. Close the tube immediately using a stopper fitted with a glass tube bent at two right angles. The solution effervesces evolving a colourless and odourless gas. Heat gently and collect the gas in 5 ml of barium hydroxide (15 g/l) TS. A white precipitate is produced which dissolves on addition of an excess of hydrochloric acid (~330 g/l) TS.

Pyrogens. Complies with 3.5 Test for pyrogens. For intravenous infusions containing 2.5% w/v or less of Sodium bicarbonate, slowly inject 10 ml per kg of the rabbit’s

weight. For intravenous infusions containing more than 2.5% w/v of Sodium bicarbonate, dilute to contain 2.5% w/v before the test.

[Note from Secretariat: the possibility to replace this test by a test for Bacterial endotoxins is under investigation.]

Assay. Titrate a suitable volume of the infusion, accurately measured, containing about 1 g of Sodium bicarbonate with hydrochloric acid (0.5 mol/l) VS using methyl orange ethanol TS as indicator. Each ml of hydrochloric acid (0.5 mol/l) VS is equivalent to 42.00 mg of $NaHCO_3$.

Sulfadoxine and pyrimethamine tablets

Draft proposal for *The International Pharmacopoeia* (June 2010). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Fax +41227914730 or e-mail to mendyc©who.int. A subscriber mailing list is now available to speed up consultation. For more information please contact bonnyw©who.int.

Category. Antimalarial.

Storage. Sulfadoxine and pyrimethamine tablets should be kept in a well-closed container, protected from light.

Additional information. Strength in the current WHO Model List of Essential Medicines: 500 mg sulfadoxine and 25 mg pyrimethamine.

Strength in the current WHO Model List of Essential Medicines for Children: 500mg sulfadoxine and 25 mg pyrimethamine.

Requirements

Comply with the monograph for "Tablets".

Definition. Sulfadoxine and pyrimethamine tablets contain Sulfadoxine and Pyrimethamine. They contain not less than 90.0% and not more than 110.0% of the amounts of sulfadoxine ($C_{12}H_{14}N_4O_4S$) and pyrimethamine ($C_{12}H_{13}ClN_4$) stated on the label.

Identity tests

A. Carry out test A.1 or, where UV detection is not available, test A.2.

A.1. Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 75 volumes of ethyl acetate R, 25 volumes of methanol R and 1 volume of glacial acetic acid R as the mobile phase. Apply separately to the plate 10 µl of each of the following two solutions in methanol R. For solution (A) shake a quantity of the powdered tablets containing about 100 mg

of sulfadoxine for 5 minutes with 20 ml, filter, and use the filtrate. For solution (B) use 5Êmg of sulfadoxine RS and 0.25 mg of pyrimethamine RS per ml. After removing the plate from the chromatographic chamber, allow it to dry in a current of air and examine the chromatogram in ultraviolet light (254 nm).

The two principal spots obtained with solution A correspond in position, appearance and intensity to those obtained with solution B.

A.2. Carry out the test as described under 1.14.1 Thin-layer chromatography, using the conditions described above under test A.1 but using silica gel R5 as the coating substance. Dip the plate in modified Dragendorff reagent TS. Examine the chromatogram in daylight.

The two principal spots obtained with solution A correspond in position, appearance, and intensity to those obtained with solution B (the spot due to pyrimethamine is faintly visible).

B. See the test described under Assay. The retention times of the two principal peaks in the chromatogram obtained with solution (1) are similar to those in the chromatogram obtained with solution (4).

Dissolution

Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms, using as the dissolution medium, 1000 ml of hydrochloric acid (0.1 mol/l) VS, and rotating the paddle at 75 revolutions per minute. At 30 minutes withdraw a sample of about 5 ml of the medium through an in-line filter and use the filtrate. Determine the content of sulfadoxine ($C_{12}H_{14}N_4O_4S$) and pyrimethamine ($C_{12}H_{13}ClN_4$) in the filtrate according to the method as described under Assay and preparing solution (4) under Assay as follows: transfer 10 ml of solution (2) and 2 ml of solution (3) to a 20-ml volumetric flask and make up to volume with hydrochloric acid (0.1 mol/l) VS.

For each of the six tablets, calculate the total amount of sulfadoxine ($C_{12}H_{14}N_4O_4S$) and pyrimethamine ($C_{12}H_{13}ClN_4$), in the medium from the results obtained. For both substances, the amount in solution for each tablet is not less than 80% of the amount declared on the label. For either substance, if the amount obtained for one of the six tablets is less than 80%, repeat the test using a further six tablets; the average amount for all 12 tablets tested is not less than 75% and the amount obtained for no tablet is less than 60%.

[Note from Secretariat: suitability of using 900 ml of dissolution medium is under investigation.]

Sulfadoxine-related substances

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (5 μm) (Phenomenex Luna® is suitable).

As the mobile phase, use a solution prepared as follows: dissolve 10 ml of glacial acetic acid R and 0.5 ml of triethylamine R in about 800 ml of water R, dilute to 1000 ml and adjust the pH to 4.2 by adding sodium hydroxide (~400 g/l) TS. Mix 850 ml of this solution with 120 ml of acetonitrile R and 30 ml of methanol R.

Use solutions (1) and (2) as described under Assay. For solution (3) transfer 1 ml of solution (1) as prepared for the assay, to a 200-ml volumetric flask and make up to volume with the mobile phase.

For solution (4) prepare a solution of sulfamethoxazole R in a mixture of equal volumes of acetonitrile R and the mobile phase to obtain a concentration of approximately 0.5 mg/ml. Transfer 2 ml of this solution and 2 ml of solution (2) to a 20-ml volumetric flask and make up to volume with the mobile phase.

Operate with a flow rate of 2 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 270 nm.

Inject separately 20 μl each of solutions (1), (3) and (4). Record the chromatograms for about 3 times the retention time of sulfadoxine (to ensure that pyrimethamine is eluted).

In the chromatogram obtained with solution (1), the following impurity peaks, if present, are eluted at the following relative retention with reference to sulfadoxine (retention time about 18 minutes): impurity A (sulfanilamide) about 0.1, impurity B about 0.2, impurity D about 0.3, impurity C about 1.4. A peak due to pyrimethamine has a relative retention of about 2.7. The test is not valid unless in the chromatogram obtained with solution (4), the resolution between the peaks due to sulfadoxine and to sulfamethoxazole (with relative retention of about 1.1 with reference to sulfadoxine) is at least 2.

In the chromatogram obtained with solution (1) the area of any peak, other than the peaks due to sulfadoxine and to pyrimethamine, is not greater than the area of the peak due to sulfadoxine in the chromatogram obtained with solution (3) (0.5%). The sum of the areas of all peaks, other than the peaks due to sulfadoxine and pyrimethamine, is not greater than twice the area of the principal peak in the chromatogram obtained with solution (3) (1.0%). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (3) (0.05%).

[Note from Secretariat: in accordance with WHO's guideline on the development of fixed-dose combinations dosage forms (least stable API controlled), and considering the ratio between the two APIs in the formulation which is 1 to 20, a test for related substances is only proposed for sulfadoxine.]

Assay

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (5 μm) (Phenomenex Luna® is suitable).

As the mobile phase, use a solution prepared as follows: dissolve 10 ml of glacial acetic acid R and 0.5 ml of triethylamine R in about 800 ml of water R, dilute to 1000 ml and adjust the pH to 4.2 by adding sodium hydroxide (~400 g/l) TS. Mix 800 ml of this solution with 200 ml of acetonitrile R.

For solution (1) weigh and powder 20 tablets and transfer a quantity of the powder containing about 0.50 g of Sulfadoxine, accurately weighed, into a 200-ml volumetric flask. Add about 70 ml of acetonitrile R and sonicate for 10 minutes. Allow to cool to room temperature, make up to volume using the mobile phase and sonicate for 10 minutes. Dilute 5 ml of this solution to 25 ml with mobile phase and filter a portion of this solution through a 0.45-μm filter, discarding the first few ml of the filtered solution. For solution (2), transfer 25 mg of sulfadoxine RS, accurately weighed, to a 25-ml volumetric flask, add about 10 ml of acetonitrile R, sonicate until dissolved and dilute to volume with the mobile phase. For solution (3), transfer 25 mg of pyrimethamine RS, accurately weighed, to a 100-ml volumetric flask, add about 35 ml of acetonitrile R, sonicate until dissolved and dilute to volume with the mobile phase. For solution (4) transfer 10 ml of solution (2) and 2 ml of solution (3) to a 20-ml volumetric flask and make up to volume with the mobile phase.

Operate with a flow rate of 2 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 227 nm.

Inject 20 μl of solution (4). The assay is not valid unless the resolution between the peaks due to sulfadoxine and to pyrimethamine, eluting in this order, is at least 5. The run time for the analyses is not less than 25 minutes.

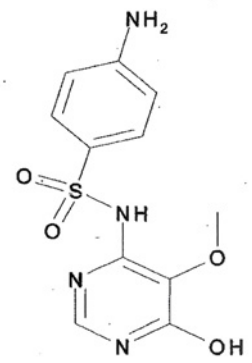
Inject alternately 20 μl each of solutions (1) and (4).

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (4), and calculate the content of sulfadoxine ($C_{12}H_{14}N_4O_4S$) and pyrimethamine ($C_{12}H_{13}ClN_4$) in the tablets.

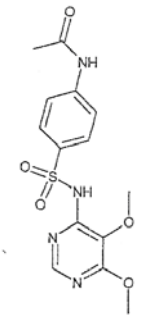
Impurities

The following list of known and potential impurities that have been shown to be controlled by the tests in this monograph is given for information.

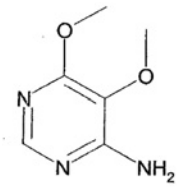
A. sulfanilamide



B. *N*1-(6-hydroxy-5-methoxy-4-pyrimidinyl) sulfanilamide



C. 4-(*p*-acetamido-benzolsulfonamido)-5,6-dimethoxy-pyrimidine



D. 4-Amino-5,6-dimethoxy-pyrimidine.

[Note from Secretariat: structures and chemical names for related substances to be confirmed.]

*****

New reagent to be added to The International Pharmacopoeia

Sulfamethoxazole R. *N''*-(5-Methyl-3-isoxazolyl)sulfanilamide: 4-amino-*N*-(5-methyl-3-isoxazolyl)benzenesulfonamide; $C_{10}H_{11}N_3O_3S$

A commercialy available reagent of suitable grade.

Description. A white or yellowish white, crystalline powder.

Solubility. Very slightly soluble in water; soluble in 50 parts of ethanol (~750 g/l) TS and in 3 parts of acetone R.

Sulfamethoxazole and trimethoprim tablets

Draft proposal for *The International Pharmacopoeia* (June 2010). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Fax +41227914730 or e-mail to mendyc@who.int. A subscriber mailing list is now available to speed up consultation. For more information please contact bonnyw@who.int.

[Note from the Secretariat: This draft text is proposed for inclusion in The International Pharmacopoeia in the context of a collaboration between WHO and the Medicines and Healthcare Products Regulatory Agency (MHRA) hosting The British Pharmacopoeia, on which this text is based.]

Category. Antibacterials.

Storage. Sulfamethoxazole and trimethoprim tablets should be kept in well-closed container, protected from light.

Additional information. Strengths in the current WHO Model List of Essential Medicines:

100 mg Sulfamethoxazole, 20 mg Trimethoprim
400 mg Sulfamethoxazole, 80 mg Trimethoprim

Requirements

Comply with the monograph for "Tablets".

Definition. Sulfamethoxazole and Trimethoprim tablets contain sulfamethoxazole and trimethoprim. They contain not less than 90.0% and not more than 110.0% of the amounts of sulfamethoxazole ($C_{10}H_{11}N_3O_3S$) and trimethoprim ($C_{14}H_{18}N_4O_3$) stated on the label.

[Note from the Secretariat: wider limits than those stated in the British Pharmacopoeia monograph (92.5%–107.5%) are proposed, to be in line with the policy and limits applied for similar dosage forms in The International Pharmacopoeia.]

Identity tests

A. Carry out test A.1 or, where UV detection is not available, test A.2.

A.1. Carry out the test as described under 1.14.1. Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 100 volumes of dichloromethane R, 10 volumes of methanol R, 5 volumes of dimethylformamide R as the mobile phase. Apply separately to the plate 5 µl of each of the following two solutions. For solution (A), add 20 ml of methanol R to a quantity of the powdered tablets containing about 400 mg of sulfamethoxazole, warm for several minutes on a water-bath with frequent shaking, cool and filter. Solution (B) use 20 mg of sulfamethoxazole RS and 4 mg of trimethoprim RS per ml of methanol R. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or in a current of cool air. Examine the chromatogram in ultraviolet light (254 nm).

The principal spots obtained with solution A corresponds in position, appearance and intensity to those obtained with solution B.

A.2. Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R5 as the coating substance and the conditions described above under test

A.1. Spray the plate with dilute potassium iodobismuthate solution TS.

The principal spots obtained with solution A correspond in position, appearance and intensity to those obtained with solution B.

B. See the test described under Assay method A. The retention times of the principal peaks in the chromatogram obtained with the test solution are similar to those in the chromatogram obtained with the reference solution.

Dissolution

For tablets containing 400 mg sulfamethoxazole and 80 mg trimethoprim. Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms, using as the dissolution medium, 900 ml of hydrochloric acid (~3.6 g/l) TS and rotating the paddle at 75 revolutions per minute. At 60 minutes withdraw a sample of about 10 ml of the medium through an in-line filter. Allow the filtered sample to cool to room temperature and dilute to 25 ml with hydrochloric acid (~3.6 g/l) TS [solution (3)]. For standard solution, use 0.36 mg of trimethoprim RS and 1.78 mg of sulfamethoxazole RS per ml of methanol R. Transfer 5.0 ml of this solution to a 50-ml volumetric flask, dilute with hydrochloric acid (~3.6 g/l) TS to volume, and mix to obtain a standard preparation having known concentrations of 0.036 mg of trimethoprim RS and 0.178 mg of sulfamethoxazole RS per ml [solution (4)]. Determine the content of sulfamethoxazole ($C_{10}H_{11}N_3O_3S$) and trimethoprim ($C_{14}H_{18}N_4O_3$) as described above under Assay method A using solution (3) and solution (4) in place of solution (1) and solution (2).

For tablets containing 100 mg Sulfamethoxazole and 20 mg Trimethoprim. Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms, using as the dissolution medium, 900 ml of hydrochloric acid (~3.6 g/l) TS and rotating the paddle at 75 revolutions per minute. At 60 minutes withdraw a sample of about 10 ml of the medium through an in-line filter [solution(3)]. For standard solution, use 0.22 mg of trimethoprim RS and 1.11 mg of sulfamethoxazole RS per ml of methanol R. Transfer 5.0 ml of this solution to a 50 ml volumetric flask, dilute with hydrochloric acid (~3.6g/l) TS to volume, and mix to obtain a standard preparation having known concentrations of 0.022 mg of trimethoprim RS and 0.111 mg of sulfamethoxazole RS per ml [solution(4)]. Determine the content of sulfamethoxazole ($C_{10}H_{11}N_3O_3S$) and trimethoprim ($C_{14}H_{18}N_4O_3$) as described above under Assay method A using solution (3) and solution (4) in place of solution (1) and solution (2).

For each of the six tablets tested, calculate the total amount of sulfamethoxazole ($C_{10}H_{11}N_3O_3S$) and trimethoprim ($C_{14}H_{18}N_4O_3$) in the medium from the results obtained. For both substances, the amount in the solution for each tablet is not less than 75% of the amount stated on the label. For either substance, if the amount obtained for one of the six tablets is less than 75%, repeat the test using a further six tablets; the average amount for all 12 tablets tested is not less than 70% and the amount obtained for no tablet is less than 55%.

[Note from Secretariat: suitability of using 500 ml of dissolution medium and possibility of shortening the sampling time are under investigation.]

Assay

Either method A or methods B and C may be applied.

A. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with particles of base-deactivated silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (5 μm) (Hypersil® BDS C18 has been found suitable).. As the mobile phase, use a solution prepared as follows: mix 1400 ml of water R, 400 ml of acetonitrile R, and 2.0 ml of triethylamine R in a 2000 ml volumetric flask. Allow to equilibrate to room temperature, and adjust with dilute glacial acetic acid (~10 g/l) TS to pH 5.9. Dilute to volume with water R, and filter through a 0.45 μm membrane.

Prepare the following solutions. For solution (1) weigh and powder 20 tablets, transfer a quantity of the powder containing about 160 mg of sulfamethoxazole, accurately weighed, into a 100 ml volumetric flask. Add about 50 ml of methanol R and sonicate, with intermittent shaking, for 5 minutes. Allow to cool to room temperature, make up to volume with methanol R, mix and filter. Transfer 5.0 ml of clear filtrate into a 50-ml volumetric flask, make up to volume with the mobile phase and mix. For solution (2), use 0.32 mg of trimethoprim RS and 1.60 mg of sulfamethoxazole RS per ml of methanol R. Transfer 5.0 ml of this solution into a 50-ml volumetric flask, make to volume with the mobile phase, and mix to obtain a standard preparation having known concentrations of 0.032 mg of trimethoprim RS and 0.160 mg of sulfamethoxazole RS per ml.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 254 nm.

Inject separately 30 μl of solutions (1) and (2) and record the chromatogram for 15 minutes. The test is not valid unless the resolution factor between the peaks due to sulfamethoxazole and to trimethoprim is not less than 5.0; the tailing factor for the trimethoprim and sulfamethoxazole peaks is not more than 2.0; and relatively standard deviation for replicate injections is not more than 2.0%.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the content of sulfamethoxazole ($C_{10}H_{11}N_3O_3S$) and trimethoprim ($C_{14}H_{18}N_4O_3$) in the tablets.

B. Weigh and powder 20 tablets. To a quantity of the powder containing 50 mg of Trimethoprim, add 30 ml of sodium hydroxide (~4 g/l) TS and extract with four quantities of 50 ml of dichloromethane R, washing each extract twice with a quantity of 10 ml of sodium hydroxide (~4g/l) TS. Combine the dichloromethane R extracts and further extract with four quantities of 50 ml of acetic acid (~60 g/l) TS. Wash the combined extracts with 5 ml of dichloromethane R and dilute the aqueous extracts to 250 ml with acetic acid (~60 g/l). To 10 ml of solution, add 10 ml of acetic acid (~60 g/l) and sufficient water to produce 100 ml and measure the absorbance of the resulting solution at the maximum at 271 nm. Calculate the amount of thrimethoprim ($C_{14}H_{18}N_4O_3$) using an absorptivity value of 20.4 ($A^{1\%}_{1\ cm}$ = 204).

C. Weigh and powder 20 tablets. Dissolve a quantity of the powder containing 500 mg of sulfamethoxazole, accurately weighed, in 60 ml of water R and 10 ml of hydrochlo-

ric acid (~420 g/l) TS. Add 3 g of potassium bromide R, cool in ice and titrate slowly with sodium nitrite (0.1 mol/l) VS, stirring constantly and determining the end-point potentiometrically . Each ml of sodium nitrite (0.1 mol/l) VS is equivalent to 25.33 mg of $C_{10}H_{11}N_3O_3S$.

Uniformity of content. Tablets containing 20 mg of Trimethoprim comply with the test for 5.1 Uniformity of content for single-dose preparations using the following method of analysis.

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given above under Assay method A.

For sample preparations, individually transfer 10 powdered tablets to 10 separate 100-ml volumetric flasks, add 50 ml of methanol R and sonicate, with intermittent shaking for 5 minutes. Allow to equilibrate to room temperature, dilute to volume with methanol R, mix and filter. Transfer 5.0 ml of clear filtrate to a 50-ml volumetric flask, dilute to volume with the mobile phase and mix. For the reference solution, use 0.20 mg of trimethoprim RS per ml of methanol R. Transfer 5.0 ml of this solution to a 50-ml volumetric flask, dilute to volume with the mobile phase and mix to obtain a reference solution with a concentration of 0.020 mg of trimethoprim RS per ml.

Measure the areas of the peak responses obtained in the chromatograms from the sample preparations and the reference solution and calculate the content of trimethoprim ($C_{14}H_{18}N_4O_3$) in the tablets.

[Note from Secretariat: suitability of a uniformity of content test for Sulfamethoxazole under investigation.]

Recent Publications, Information and Events

Restricted and banned pharmaceuticals

The recently published WHO document *Pharmaceuticals: Restrictions in use and availability* provides biennial updates to the *United Nations Consolidated List of Products whose Consumption and/or Sale have been Banned, Withdrawn, Severely Restricted or Not Approved by Governments - Pharmaceuticals.* Information contained in this document includes basic drug product information, countries that have taken regulatory actions towards the product, and the rationale for the restrictions.

The document serves as a reference for the pharmaceutical community, including drug regulators, and those interested in the safe and rational use of drugs, to become better informed about regulatory actions in different parts of the world.

Information for this document is provided by voluntary contributions from countries participating in the WHO Programme for International Drug Monitoring. In addition, relevant information from other drug-related documents issued by the World Health Organization, including the WHO Drug Alerts, WHO Pharmaceuticals Newsletter and the *WHO Drug Information* is also included. It should be noted that this information is neither exhaustive nor comprehensive. The decisions taken by a limited number of governments on a specific product may not be representative of the positions of other governments.

Reference: World Health Organization. *Pharmaceuticals: Restrictions in use and availability* at: http://www.who.int/medicines/publications/restricted_list/en/index.html

Hands–on approach to pharmaceutical policy

Pharmaceutical policy is that part of health policy that aims at increasing access to safe, effective and affordable medicines for all patients. However, there are many obstacles against achieving these goals. *A practical approach to pharmaceutical policy* offers policy makers a hands-on approach, tested in the World Bank's field work in many countries, for assessing the pharmaceutical sector, recognizing typical "patterns of dysfunction" and developing strategies to quickly deal with the most urgent problems while at the same time building a platform for sustainable long term policy. It offers examples from a variety of low- and middle income countries and provides practical assessment tools for policy makers. The book ends with an outlook on future developments in this complex policy field.

Reference: *A practical approach to pharmaceutical policy* . Available on-line at: http://issuu.comworld.bank.publications/docs/9780821383865 or to order at http://publications.worldbank.org/

Certification programme for WHO Drug Dictionary

Uppsala Monitoring Centre (UMC), a Collaborating Centre of the World Health Organization, through its Global Intelligence Network for Benefits and Risk in Medicinal Products, has launched a certification programme that helps software developers integrate the WHO Drug Dictionary Enhanced quickly and easily.

UMC's new certification offers a set of test cases, with associated acceptance

criteria, to indicate whether implementation processes are accurate. It also offers software developers free training and a software development kit, including documentation and example programmes. Software products that currently include WHO coding implementations can immediately apply for certification using the cases provided to determine when they are ready for the certification review. The value of coding medical product information correctly in pharmacovigilance and clinical trials cannot be overstated. Companies that enrol in the programme can use its templates and examples as blueprints for developing solutions that fulfil user requirements.

Reference: Uppsala Monitoring Centre, 14 June 2010. http://www.who-umc.org

New WHO quality assurance guidelines

The latest report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations is now available. During its Forty-fourth meeting, experts adopted 42 new monographs for inclusion in *The International Pharmacopoeia* and nine International Chemical Reference Standards. In addition, the following seven new quality assurance guidelines were adopted and are included in the report:

- WHO good practices for pharmaceutical quality control laboratories (Annex 1).
- WHO good manufacturing practices for active pharmaceutical ingredients (Annex 2).
- WHO good manufacturing practices for pharmaceutical products containing hazardous substances (Annex 3).
- WHO good manufacturing practices for sterile pharmaceutical products (Annex 4).
- WHO good distribution practices for pharmaceutical products (Annex 5).
- Guidelines on the requalification of prequalified dossiers (Annex 6).
- Guidelines for the preparation of a contract research organization master file (Annex 7).

Reference: World Health Organization. Medicines Quality Assurance web site at http://www.who.int/medicines/areas/quality_safety/quality_assurance.

Good procurement practices for ACTs

The WHO Manual, *Good Procurement Practices for Artemisinin-based Antimalarial Medicines,* aims to provide guidance for the procurement of safe, effective and quality-assured artemisinin-based antimalarial medicines. The target audience for this manual includes all health officers and supply chain managers in the public and private sectors responsible for procuring and distributing artemisinin-based antimalarial medicines.

In this manual, practical information from several publications related to quality of medicines are summarized, with the aim of improving understanding of medicines recommended in evidence-based treatment guidelines, common problems with the quality of artemisinin-based antimalarial medicines, pharmaceutical product quality, and the role, principles and methods of quality control testing.

Reference: World Health Organization. *Good Procurement Practices for Artemisinin-based Antimalarial Medicines* at http://whqlibdoc.who.int/publications/2010/9789241598927_eng.pdf