

# WHO Drug Information

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## **Announcement**

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**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 Programmes

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## WHO Prequalification of diagnostics, medicines and vaccines

World Health Organization (WHO) pre-qualification is a highly visible service having an immediate impact for countries. WHO prequalification programmes for diagnostics, medicines and vaccines operate on similar principles and offer a valuable assurance of quality. Each programme regularly conducts technical and performance reviews to identify potential gains in efficiency.

### Diagnostics

In recent years, the number of diagnostic products for priority diseases such as HIV, TB and malaria has increased. Of WHO's 193 Member States, fewer than one-third have a regulatory system in place and even where regulations for diagnostics exist, they are often not enforced.

Approximately 85% of applications submitted to the WHO Programme for Diagnostics Prequalification are for products made in less stringently regulated countries, particularly in Asia. Moreover, as the target markets for these diagnostics are resource-limited countries, the manufacturers concerned do not consider that they need to obtain licensing from a stringent regulatory authority. The Programme targets its assessment efforts at such products, paying particular attention to appropriateness for use in resource-limited settings and advocating for the development of innovative diagnostics for such settings.

The WHO Programme for Diagnostics Prequalification bases its activities on

international, harmonized quality and safety standards and seeks to ensure that other agencies and organizations promote and adhere to these standards. The Programme is also working with United Nations (UN) partners and procurement organizations to harmonize procurement requirements for diagnostics. In areas where no prequalified products yet exist, it advises on purchase of non-prequalified products.

### Capacity building

The WHO Programme for Diagnostics Prequalification is working with Burkina Faso, Côte d'Ivoire, South Africa and Tanzania to strengthen implementation of regulations concerning registration and licensing of diagnostics and to establish systems for postmarketing surveillance. (Activities will be extended to China during 2010.)

Guidance documents highlighting requirements for inspections and quality management systems are being finalized for use by manufacturers seeking to obtain WHO prequalification.

### Cost effectiveness

Prequalification of diagnostics stimulates innovation and helps create a secure market for good-quality, safe and appropriate diagnostics that would otherwise not be accessible. For example, prequalification of diagnostics stimulates development of technologies such as rapid tests, appropriate for use at primary health care level and by non-lab technicians (which promotes task shifting). During the past four years, the UN and Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) procurement of HIV and malaria rapid tests has ranged between 10 and 18 million tests annually.

WHO facilitates access to safe, appropriate diagnostics of good quality at reduced cost, saving money that can be used to purchase additional diagnostics or invested in other health care interventions. In the USA, for example, a rapid HIV test costs around ten US dollars, while the UN/WHO price is around one US dollar. Savings are also generated since health care costs associated with poor-quality diagnostics are reduced. Additionally, the value of laboratory services is increased through reliable accurate diagnosis and the efficacy of treatment programmes is improved. More patients can therefore be treated.

### Information and guidance

Information on WHO's procedure for prequalifying diagnostics, together with guidance and application forms, and a wide range of technical documents and reports, can be found at: [http://www.who.int/diagnostics\\_laboratory/evaluations/en/](http://www.who.int/diagnostics_laboratory/evaluations/en/) and the WHO Programme for Diagnostics Prequalification web site is at [http://diagnostics\\_laboratory.technology/](http://diagnostics_laboratory.technology/)

## Medicines

WHO's list of prequalified medicines is used by the GFATM, UNICEF, the World Bank, international nongovernmental organizations (NGOs) and, increasingly, by government procurement agencies as a basis for many procurement decisions. Similarly, the *Model Quality Assurance Guideline* developed by the WHO Prequalification of Medicines Programme is used by the US President's Emergency Plan for AIDS Relief (PEPFAR) and the World Bank to guide organizations that procure medicines in improving their quality systems.

More generally, the WHO Prequalification of Medicines Programme has done much to ensure that medicines procured by UN agencies and other organizations meet

international, harmonized quality and safety standards. This includes working with the GFATM and procurement organizations to harmonize procurement and quality assurance requirements. In areas for which no prequalified product yet exists, and on behalf of UN partners, the WHO Prequalification of Medicines Programme organizes, upon request, expert assessment reviews to advise on levels of risk associated with purchase of non-prequalified products. It also advises UNFPA and the WHO Department of Reproductive Health and Research on methods for prequalifying condoms and intrauterine devices.

Concurrently, activities to prequalify quality control laboratories are also of great value to agencies and organizations who provide or fund significant quantities of medicines for disease treatment programmes. National prequalified laboratories enable rapid and reliable analysis of medicines quality analysis close to locations where the medicines are in actual use. By 2009, 11 laboratories have been prequalified and a further 28, most of which are in Africa, have expressed interest in becoming prequalified or are undergoing assessment.

The WHO Prequalification of Medicines Programme is closely linked to WHO's quality assurance normative work and provides "real life" feedback for development of pharmaceutical norms and standards. The Programme is further linked to WHO pharmacovigilance activities and monitoring of adverse drug reactions (ADRs) provides follow-up on the quality and safety of prequalified medicines. Joint planning and implementation of prospective proactive safety monitoring for selected prequalified new products (such as an amodiaquine + artesunate fixed-dose combination product for malaria) will be an important source of information.

### Capacity building

Unlike other regulatory options (such as product approvals/registration by a stringent regulatory authority, including US FDA tentative approval), the WHO Prequalification of Medicines Programme is open to participation of regulators from developing countries. For example, these regulators can actively participate in dossier assessments and inspections.

Additionally, the Programme undertakes considerable capacity building through its provision of standards, guidance and training to assessors and inspectors regarding regulatory assessment of the quality, safety and efficacy of medicines. Most of the training workshops organized in developing countries are also open to participants from local industry. Training to date has focused on pharmaceutical development of quality products and on quality of manufacture. In 2009, 12 training courses were organized for regulators and local industries and a further five training courses co-organized or supported for around 760 participants in total.

On-the-job training is offered in the form of a unique three-month rotational post at WHO, Geneva, open to promising trainees from developing country national medicines regulatory authorities (MRAs). Developing country manufacturers of products of high public health value (such as second-line TB medicines and injectable antimalarials) receive tailored technical assistance to help them bring the quality of their medicines production up to international standards. In the case of technically complex products, the Programme provides regulatory advice to applicants, for example, on conducting bioequivalence studies.

The WHO Prequalification of Medicines Programme makes ample information about prequalified medicines (including evaluation/inspection outcomes) publicly available (<http://www.who.int/prequal/>).

The above activities contribute to:

- more effective regulation and production of medicines of assured quality;
- more rapid development of new, quality products; faster regulatory approval of products, and
- identification of norms and standards needed for development by the WHO Expert Committee on Specifications for Pharmaceutical Preparations.

### Cost effectiveness

WHO prequalification of medicines for HIV/AIDS, in particular, has stimulated generic production of quality medicines and global competition, serving to lower medicines prices and enabling more patients to be treated. The prices negotiated by the Clinton HIV/AIDS Initiative, with the support of UNITAID and government partners, for fixed-dose combination (FDC) paediatric antiretroviral treatment are a case in point.

An external business plan completed for the WHO Prequalification of Medicines Programme in August 2009 comments, "It is clear that in the context of today's disease landscape the Programme has a vital, pivotal and ongoing role". It projects an economic return on investment of 170:1 for the programme for the period 2009–2013. This estimate is based on:

- projected availability of global funding for procuring medicines for treating HIV/AIDS, TB and malaria;
- projected prequalification of 105 additional medicines, around 90% of which will be generic medicines, and
- projected estimated impact on additional volume of medicines that can be purchased as a result of increased competition among generics.

Sampling and quality control testing undertaken by the WHO Prequalification

of Medicines Programme has demonstrated that the failure rate among WHO prequalified medicines is exceptionally low (<3%). To date, no critical failures have appeared among sampling and testing results. The results underscore that, provided procurement and distribution practices are sound, medicines prequalified by WHO can be viewed with confidence, by health workers, patients and donor agencies alike.

### Information and guidance

All documentation regarding the WHO Prequalification of Medicines Programme is posted at: <http://www.who.int/prequal/default.htm> and is available in CD-ROM and DVD format. Programme procedures and technical guidelines have all been adopted by the WHO Expert Committee on Specifications for Pharmaceutical Products and are therefore available in WHO's *Technical Report Series* in hard copy and electronic versions. The WHO Prequalification of Medicines Programme web site is at <http://www.who.int/prequal/>

## Vaccines

Vaccines prequalified by WHO are used in 112 countries to immunize 53% of the global birth cohort each year. By the end of 2009, 104 vaccines from 26 manufacturers had been prequalified by WHO. The starting point for WHO vaccines prequalification is the licensing of a vaccine by a national regulatory authority (NRA) that has been audited by WHO and shown to meet international standards for regulatory oversight.

The added value of WHO prequalification is that it provides objective and independent evidence to UN procurement agencies that the products concerned are suitable for use in immunization programmes supported by UN supply. National licensure, even by developed country regulators such as the US FDA and European Medicines Agency (EMA), considers only whether vaccines are

suitable for use by immunization programmes covered within their jurisdiction.

Vaccines supplied to immunization programmes supported by the UN must be safe and effective in conditions that differ from those in developed countries. Illustrative examples relate to: (i) the immunization schedule and (ii) the temperature-controlled supply chain. For UN supply, immunization is based on the Expanded Programme on Immunization (EPI) 2, 3, 4 months schedule which includes oral poliovirus vaccine and whole-cell pertussis.

The temperature-controlled supply chain required for vaccines is more fragile in countries receiving vaccines through UN supply than in developed countries. WHO Vaccines Prequalification thus pays special attention to the thermostability profile of vaccines. For example, a rotavirus vaccine product was originally developed for the US market. Review by WHO Vaccines Prequalification discovered that even brief heat exposure resulted in destruction of one of the strains in the vaccine. WHO requested the manufacturer to introduce additional shipping precautions and stimulated the company to create a development programme for a more heat-resistant vaccine. In 2009, the manufacturer announced the creation of a new vaccine research institute in India to develop vaccines that are optimized for use in developing countries.

### Capacity building

WHO Vaccines Prequalification conducts an audit of NRA functionality before accepting an application from a vaccine producer which includes identification of regulatory gaps. Such audits enable NRAs to leverage increased human and financial resources from their governments. WHO Vaccines Prequalification has thus stimulated increased global capacity for adequate regulatory oversight of vaccines in countries such as

Brazil, Cuba, India, Indonesia, Senegal and Thailand.

The audit process requires that WHO establish the first international benchmarks of regulatory functions. These are now being used by developed country authorities, such as EMA, for inter-authority reviews within their jurisdictions. Furthermore, the WHO audit process provides countries with an objective institutional development plan for regulatory functionality that can be incorporated in a strategy for health systems strengthening.

### **Cost effectiveness**

Prequalification of vaccines gives manufacturers in emerging economies — whose prices may be lower than those of manufactures in developed countries — access to international markets. This occurs both directly, through UN procurement, and indirectly when national procurement agencies in middle-income countries use the WHO list of prequalified vaccines to select vaccines for national procurement. WHO Vaccines Prequalification assists emerging economy manufacturers to attain international standards of quality. This facilitates entry into the global market and additionally acts as an incentive to developed country manufacturers to lower the prices of their vaccine

products. Evidence from UN procurement agencies, such as UNICEF, shows how the entry of WHO prequalified vaccines into the market serves to lower vaccine prices. Further, WHO Vaccines Prequalification contributes to global vaccine security by expanding the number of quality-assured manufacturers per vaccine type.

### **Information and guidance**

The WHO procedure for prequalifying vaccines is published as: *Assessment of the Acceptability, in Principle, of Vaccines for Purchase by United Nations Agencies* (WHO/IVB/05.19). A separate document provides guidance to manufacturers on how to produce a good product summary file: *Guideline for Preparation of Vaccine Product Summary File for Vaccine Prequalification* (WHO/IVB/06.16). Both documents exist in hard copy and are posted on the WHO vaccines web site ([www.who.int/immunization](http://www.who.int/immunization)). Additional documents are being prepared: *Guidance for Master Formula*, *Guidance for Environmental Monitoring of Aseptic Areas*, *Guidance for Clinical Trials*. Each of these documents are or will be used principally by manufacturers, but they are also of relevance to governments and other interested parties. The WHO Vaccines Prequalification web site is at <http://www.who.int/immunization>

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## **WHO Prequalification of Medicines Programme**

### **Inspection of finished pharmaceutical product manufacturers**

Substandard, counterfeit and adulterated medicines have far-reaching consequences for patients and the quality of medicines remains a concern. Some estimates put counterfeits at more than 10% of the global medicines market and an estimated 25% of medicines con-

sumed in developing countries are believed to be counterfeit. A WHO survey of reports on counterfeit medicines from 20 countries in the period from January 1999 to October 2000 found that 60% of cases occurred in poor countries and 40% in industrialized countries (1–2). The Pharmaceutical Society of Nigeria reports that at around 70% of medicines circulating in that country may be counterfeit (3). Many cases of substandard medicines

**Table 1. Manufacturing sites inspected by WHO in 2008–2009**

	China	Egypt	India	Morocco	South Africa	Total
2008	3	1	16	1	1	<b>22</b>
2009	1	0	22	0	2	<b>25</b>
<b>Total</b>	<b>4</b>	<b>1</b>	<b>38</b>	<b>1</b>	<b>3</b>	<b>47</b>

could be prevented through effective implementation and enforcement of legislation requiring that medicines be produced and controlled in compliance with good manufacturing practices (GMP).

The World Health Organization (WHO) defines GMP as “that part of quality assurance that ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization”. GMP comprises the standards under which the production and control of pharmaceutical products should take place. Specific risks associated with the manufacture and control of pharmaceutical products are essentially cross-contamination and mix-ups (4).

One component of the extensive evaluation process of the United Nations Pre-qualification of Medicines Programme managed by WHO focuses on the inspection of finished pharmaceutical product manufacturing facilities. An inspection team is made up of a WHO inspector plus an appointed inspector from a member

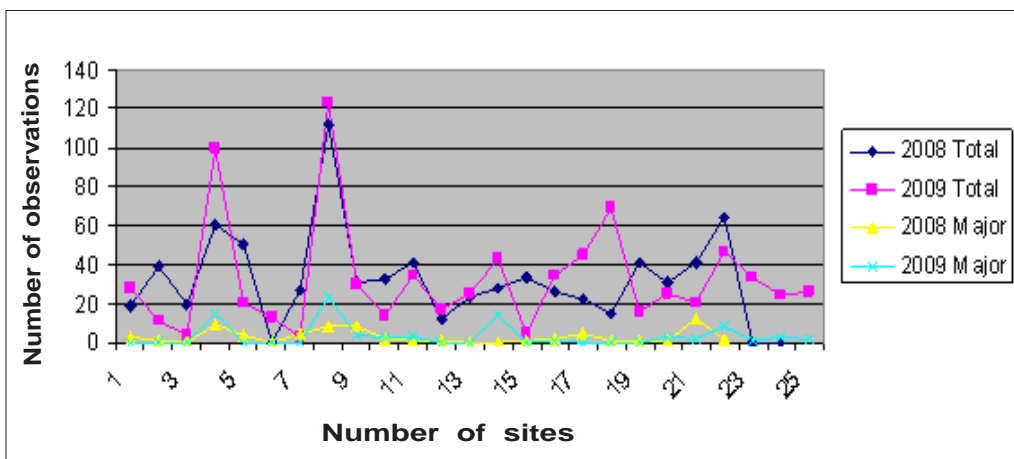
country of the Pharmaceutical Inspection Cooperation Scheme (PIC/S). During inspections, manufacturers are assessed for compliance with WHO GMP. Inspectors further verify the reliability of data submitted in product dossiers against the original data on site (5).

The first inspections were carried out in June 2001 and focused on manufacturers of HIV/AIDS medicines. Since then, the Programme has expanded and now includes products used in the treatment of malaria, tuberculosis, influenza and reproductive health products. During 2008 and 2009, several site inspections were carried out in China, Egypt, India, Morocco and South Africa.

The location of manufacturing sites inspected in 2008 and 2009 is set out in Table 1, and the number of inspections by product range (disease group) in Table 2. In the majority of cases, inspections were carried out in India focusing on dosage forms used in the treatment of HIV/AIDS. In 2009, four inspections were carried out at sites producing reproductive health products, and one each at sites produc-

**Table 2. Product range by disease group**

Product	2008	2009	Total
HIV/AIDS	10	9	<b>19</b>
Tuberculosis	6	5	<b>11</b>
Malaria	5	4	<b>9</b>
HIV/AIDS and malaria	1	0	<b>1</b>

**Figure 1. Number of observations by site**

ing HIV/AIDS and influenza products, antituberculosis and HIV/AIDS products; and HIV/AIDS, antituberculosis and malaria products.

Co-inspectors were appointed from Australia (5), Denmark (2), Estonia (5), France (12), Hungary (3), South Africa (2), Switzerland (4) and the United Kingdom (7). In seven cases, sites were inspected by a team of inspectors from WHO without a co-inspector. These were special inspections or investigations.

Figure 1 shows the number of total and major deficiencies (observations) recorded in each of the sites inspected in 2008 and 2009. Overall, the trend shows that the average number of observations per site remains more or less the same over the last two years and that there was a small amount of major non-compliance in almost all cases. This does not mean that there is no improvement in compliance with GMP — since the same sites were not necessarily inspected year to year.

Examples of major non-compliance in manufacturing sites of anti-malaria products included lack of validation, insufficient control over deviations, lack of in-line clearance procedures with a

possibility in mix-ups and a possibility of cross contamination due to lack of appropriate cleaning. In some manufacturing facilities, sampling and testing was deficient in ensuring the identity of material used in production (including active pharmaceutical ingredients). In the case of sterile products, the sterilization process was not validated in some cases and the aseptic technique and media fill was inadequate. An unacceptable risk of product contamination was also identified.

Examples of major non-compliance in manufacturing sites of antituberculosis products included inappropriate management of deviations and changes that may have an impact on product quality. In one site, all deviations inspected showed that even as a deviation was initially reported by an operator, the deviation was completed prior to authorization by the production supervisor, manager, director, and quality assurance. The company further failed to appropriately implement the written programme for ongoing stability testing. Because there was a backlog in testing stability samples — in some cases up to 90 days delay — the stability laboratory had to assist the quality control laboratory to test finished products for final release.

During one inspection, in several identified cases, there was no record of an out of specification (OOS) result having been reported by the analysts and in several cases no investigation of reported OOS results was performed.

Examples of major non-compliance in manufacturing sites of HIV/AIDS products included insufficiently documented evidence that appropriate process validation was carried out. This was due to inappropriate management and control of quality control laboratory generated data. There was lack of traceability of data and source data as the company failed to retain and maintain electronically generated data and results in an accessible form. In several cases, chromatograms demonstrated peaks and baselines which were essentially similar if not identical, and retention times were identical. No electronic source data had been retained in any way to enable verification of data.

Examples of major non-compliance at manufacturing sites of reproductive health products included lack of control of changes. In one case, the change control procedure appropriately described the process to be followed. However, there were approximately 200 open change request forms corresponding to an approximate five month period. In several cases, there was insufficient air filtration (supply and exhaust) and pressure cascades, inappropriate gowning by operators and lack of containment to ensure safety of operators, products and protection of the environment. In several

cases; room pressures measured were OOS and did not comply with the design room pressures. In one case, batches of product that failed the sterility test were kept on hold for almost a year and were not destroyed.

In several cases during site inspections of reproductive health products, the observations were so many that it was not possible to classify the observations.

In conclusion, a higher number of non-compliance events were observed at manufacturing sites of reproductive health products than any other manufacturers.

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## Corrigendum

The following correction refers to the article entitled "WHO Prequalification of Medicines Programme: facts and figures for 2009" found in the section "Inspections" on page 4 of *WHO Drug Information*, Volume 24, Number 1.

*Prequalification of Medicines Programme inspectors carried out 52 inspections in nine countries: 27 finished pharmaceutical product manufacturing sites, seven of API manufacturing sites, ten of contract research organizations (CROs) and eight of pharmaceutical quality control laboratories (including two pre-audit inspections). The majority of inspections were carried out in India, followed by China, Singapore, South Africa, Ukraine and Viet Nam.*

# Regulatory Harmonization

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## Optimization of medicines regulatory authority web sites

The objective of every medicines regulatory authority (MRA) is to ensure that all medicines marketed in the respective country are of assured quality, safety and efficacy, and are accompanied by appropriate information to promote their rational use. Therefore, the existence of a reliable and accessible web site plays a vital role in providing independent regulatory information.

A study carried out by the World Health Organization in 2001 on the status of 51 MRA web sites operating nationally has now been updated and a report published which shows that the number of web sites has risen to 116 (1). Most criteria, such as frequency of updates, pharmacovigilance information and regulatory guidance for medicines marketing authorization have improved substantially, although navigability of web sites is still problematic. Overall, development of new MRA web sites over the past eight years is impressive and the number has more than doubled. It is remarkable how countries from all income categories have made efforts to launch and maintain web sites that provide the general public, health professionals and industry with good-quality regulatory information.

### Review of web sites: 2001 and 2009

The Internet is a tool used extensively by patients, health professionals and pharmaceutical companies to obtain information on pharmaceutical products. Through the Internet, medicines regulatory authorities (MRAs) can provide access to regulations and requirements for ensuring the quality, safety and efficacy of medicines, regulatory guidance on marketing and information on approved products.

The present review updates a WHO study undertaken in 2001 to assess the quality of information available on 51 MRA web sites [2–3]. Since then, there has been a major increase in the number of countries that maintain a web site. The 2001 study demonstrated that many web sites provided limited information that was often not easy to access and almost 60% did not have an adequate search engine.

Over 80% of web sites had inadequate sections on medicines safety alerts and reporting of adverse drug reactions and more than 50% of web sites did not provide access to information on registered medicines.

The information gap about legitimately marketed medicines and restricted/cancelled marketing authorizations is of concern to many healthcare professionals and researchers. A number of publications have expressed the need for transparency and the provision of good quality health information by medicines regulatory authorities [4–7].

In 2008, a study of Australia, Canada, European Medicines Agency, France, New Zealand, United Kingdom and USA web sites assessed the availability of information [8]. It concluded that the type and amount of information varied widely, with several MRAs not making basic

information publicly available. The European Medicines Agency alone published complete information on cancelled marketing authorizations and the Health Canada web site was the only site to offer full access to pharmacovigilance data. No web site released the periodic safety update reports that companies have to provide to MRAs. The study criticized the lack of openness and called for increased transparency and independence of regulatory authority activities [8].

The general public is also a stakeholder in the debate on the relative lack of certain types of information related to medicines. In 2007, it was reported that 20% of Finnish medicine users name the Internet as a source of information, with up to 30% in the age group 15–34 years of age [9]. Medical doctors, pharmacists and patient information leaflets (PILs) were reported as the most reliable sources of medicines information, followed by MRAs, nurses, information leaflets and medicine guides and textbooks. However, only 24–43% of medi-

cine users evaluated the Internet as reliable. For example, in Singapore in 2009, 15% of consumers reported having used the Internet as a medicines information source, with 34% having problems finding reliable and accurate information [10]. Among physicians in Thailand, 29% of faculty and 25% of residents used the Internet as the first means through which they learnt of new medicines [11].

As a consequence of increased demand, the amount and quality of information available on the Internet has increased enormously over the past eight years. However, it is not clear which countries are leading and which subject areas still need strengthening on their web sites.

The objective of the present study (1) is to provide an update on the status of MRA web sites, the number of MRAs that have web sites, and show any association with income group classification of the country. It reviews the accessibility, completeness and quality of information on MRA web sites.

**Table 1: Numbers and percentages of countries with identified MRA web site by WHO Region**

Region	Number of MRA web sites 2001*	%	Number of MRA web sites 2009	%
AFR	4 of 46	9	16 of 46	35
AMR / PAHO	7 of 35	20	20 of 35	57
EMR	1 of 21	5	11 of 21	52
EUR	29 of 54	54	47 of 54	87
SEAR	3 of 11	27	8 of 11	73
WPR	9 of 29	31	14 of 29	48
<b>Totals:</b>	2001: 53 of 196 potential websites (27%) 2009: 116 of 196 potential websites (59%)			

\*The list of countries for 2001 has been adjusted to the 2009 list.

Abbreviations: AFR: WHO Region for Africa; AMR / PAHO: Region for the Americas / Pan American Health Organization; EMR: Region for the Eastern Mediterranean  
EUR: Region for Europe; SEAR: Region for South-East Asia; WPR: Region for the Western Pacific

**Identification of available web sites**

In 2009, 116 MRA web sites were identified. The percentage of countries with web sites has more than doubled from 27% in 2001 to 59% in 2009. Table 1 shows the increase in numbers and percentage of countries with identified MRA web sites by WHO Region.

**Scores**

Table 2 shows scoring for 51 countries assessed in 2001 together with results from 2009 for the same countries.

Many researchers have argued that the provision of information by MRAs is inadequate [3–4, 6, 11, 14]. However, the situation has improved significantly over the past eight years, especially on potentially confidential and controversial subjects such as clinical trial data and medicines safety information. However, although this is a positive development there is still room for improvement as only 43% of web sites provide at least satisfactory information on pharmacovigilance. In addition, improvement could be made

**Table 2: results of scoring for 51 countries assessed in 2001 and 2009**

Criteria	2001 in %			2009 in %		
	Inadequate	Inter- mediate	good	Inadequate	Inter- mediate	good
user-friendliness	22	49	29	10	47	43
site map	61	12	28	20	10	71
navigability	10	31	59	12	53	35
speed*	18	26	57	37	31	33
search	57	18	26	14	73	14
update	55	8	37	16	14	71
mission statement	18	51	31	24	14	63
contact information	29	33	37	10	57	33
organizational structure	31	28	41	18	55	27
services	71	10	20	12	29	59
news, events & meetings	53	20	28	29	45	25
pharmacovigilance	80	8	12	18	39	43
feedback form	57	14	29	51	8	41
regulatory guidance, legislation & regulation	33	39	28	10	45	45
instructions for marketing applicants	28	26	47	22	29	49
medicinal products	53	33	14	35	27	37
licensed manufacturers	84	10	6	59	4	37
import & export	80	12	8	35	47	18
approved wholesalers distributors, pharmacies	75	20	6	75	8	18
statistics: medicines consumption	88	4	8	78	8	14
statistics on country profile	88	0	12	82	14	4
statistics on MRA activities	75	4	22	59	10	31
links	51	18	31	25	25	49
publications	59	20	22	37	25	37
languages				33	28	39

\* The speed of the MRA web sites of Morocco and Thailand could not be assessed using the web site optimization tool.

by the online publication of data that is being provided on paper. PILs and SPCs were only available on a third of reviewed web sites whereas this information could be very valuable for consumers and health care professionals alike [9–11].

In assessing the World Bank income group classification of the country, it became clear that national income has a strong association with the existence of MRA web sites. However, a number of low income countries also have web sites and the improvement in content of web sites is striking. Whereas many web sites provided no more than contact information and an organigram in 2001, current web sites include comprehensive pages on legislation and regulatory guidance, information on medicinal products and pharmacovigilance. User-friendliness of the regulatory web sites has improved considerably, although many could still profit from some improvement in attractiveness, site mapping and navigation.

Efficient search engines and subject indexes are often missing. Although the percentage of countries with intermediate search engines increased from 18% to 73%, only 14% of countries really allow thorough searching of the web site.

Good examples of user-friendly web sites that were easy to navigate include the United Kingdom and Denmark [12] and Ireland and India web sites scored intermediate on navigability which is reflected in difficulties users had when searching web sites for more specific information. It is not always certain that users will have the persistence needed to find information being sought. Many MRAs provide enormous amounts of information and documents on their web sites but navigability is often poor. The importance of a good infrastructure, the availability of a site map and efficient search engines should not be underestimated.

Updating of web sites has improved significantly. Fifty-five per cent of web sites reviewed in 2001 were not updated during the previous year but this percentage has declined to 16% in 2009. Currently, 71% of web sites studied are being updated monthly.

The greatest improvement has been made in the section on pharmacovigilance. Over 80% of web sites assessed in 2001 did not provide adequate information on how to report adverse drug reactions nor publish safety alerts. In 2009, only 18% of web sites scored inadequately on this item and 41% of web sites had good sections on pharmacovigilance. As an example, the United States Food and Drug Administration web site gives very comprehensive pharmacovigilance data.

Overall, web sites that were already online in the earlier survey are more likely to have improved both in terms of quality and content. In addition, the countries that had web sites in 2001 were mainly high income countries and score better in general. On the other hand, a number of new web sites have been identified that exceed some of the older web sites. Particularly good examples of new MRA web sites are those of Sudan and Argentina.

In countries where ministries of health have regulatory functions, specific web pages for regulatory activities should be launched. Web sites should endeavour to improve their accessibility by establishing links from other sites, such as the relevant governmental authorities and institutions (ministries of health, commerce and trade, customs authorities, etc.), general health information sites and regional medicines regulatory authority sites.

In conclusion, the 51 countries that have maintained web sites over the past eight years show considerable improvement in the content and comprehensiveness of

information provided. Such subjects as site maps, updates and mission statements that were missing in 2001 are now almost fully covered. On the other hand, there is still room for improvement on all topics, including key subjects such as regulatory guidance, pharmacovigilance and registries of medicinal products.

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## Medicines regulatory authority web sites

### *WHO Region for Africa*

Algeria	<a href="http://www.ands.dz">http://www.ands.dz</a>
Botswana	<a href="http://www.moh.gov.bw">http://www.moh.gov.bw</a>
Burkina Faso	<a href="http://www.sante.gov.bf">http://www.sante.gov.bf</a>
Ethiopia	<a href="http://www.daca.gov.et">http://www.daca.gov.et</a>
Ghana	<a href="http://www.fdbghana.gov.gh">http://www.fdbghana.gov.gh</a>
Kenya	<a href="http://www.pharmacyboardkenya.org">http://www.pharmacyboardkenya.org</a>
Mali	<a href="http://www.dirpharma.org">http://www.dirpharma.org</a>
Mauritius	<a href="http://www.gov.mu">http://www.gov.mu</a>
Namibia	<a href="http://www.nmrc.com.na">http://www.nmrc.com.na</a>
Nigeria	<a href="http://www.nafdacnigeria.org">http://www.nafdacnigeria.org</a>
Rwanda	<a href="http://www.moh.gov.rw">http://www.moh.gov.rw</a>
Senegal	<a href="http://www.sante.gouv.sn">http://www.sante.gouv.sn</a>
South Africa	<a href="http://www.mccza.com">http://www.mccza.com</a>
Swaziland	<a href="http://www.gov.sz">http://www.gov.sz</a>
Uganda	<a href="http://www.nda.or.ug">http://www.nda.or.ug</a>
United Republic of Tanzania	<a href="http://www.tfda.or.tz">http://www.tfda.or.tz</a>
Zimbabwe	<a href="http://www.mcaz.co.zw">http://www.mcaz.co.zw</a>

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**Medicines regulatory authority web sites (continued)***WHO Region for the Americas*

Argentina	<a href="http://www.anmat.gov.ar">http://www.anmat.gov.ar</a>
Bahamas	<a href="http://www.phabahamas.org">http://www.phabahamas.org</a>
Bolivia	<a href="http://www.sns.gov.bo">http://www.sns.gov.bo</a>
Brazil	<a href="http://www.anvisa.gov.br">http://www.anvisa.gov.br</a>
Canada	<a href="http://www.hc-sc.gc.ca">http://www.hc-sc.gc.ca</a>
Chile	<a href="http://www.ispch.cl">http://www.ispch.cl</a>
Colombia	<a href="http://www.invima.gov.co">http://www.invima.gov.co</a>
Costa Rica	<a href="http://www.ministeriodesalud.go.cr">http://www.ministeriodesalud.go.cr</a>
Cuba	<a href="http://www.cecmec.sld.cu">http://www.cecmec.sld.cu</a>
Dominican Republic	<a href="http://www.drogasyfarmacias.gov.do">http://www.drogasyfarmacias.gov.do</a>
Guatemala	<a href="http://portal.mspas.gob.gt">http://portal.mspas.gob.gt</a>
Guyana	<a href="http://www.health.gov.gy">http://www.health.gov.gy</a>
Honduras	<a href="http://www.dgrs.gob.hn">http://www.dgrs.gob.hn</a>
Jamaica	<a href="http://www.pcoj.org">http://www.pcoj.org</a>
Mexico	<a href="http://www.cofepris.gob.mx">http://www.cofepris.gob.mx</a>
Panama	<a href="http://www.minsa.gob.pa">http://www.minsa.gob.pa</a>
Paraguay	<a href="http://www.mspbs.gov.py">http://www.mspbs.gov.py</a>
Peru	<a href="http://www.digemid.minsa.gob.pe">http://www.digemid.minsa.gob.pe</a>
Trinidad and Tobago	<a href="http://www.health.gov.tt">http://www.health.gov.tt</a>
United States of America	<a href="http://www.fda.gov">http://www.fda.gov</a>
Uruguay	<a href="http://www.msp.gub.uy">http://www.msp.gub.uy</a>
Venezuela	<a href="http://www.inhrr.gov.ve">http://www.inhrr.gov.ve</a>

*WHO Region for the Eastern Mediterranean*

Egypt	<a href="http://www.eda.mohp.gov.eg">http://www.eda.mohp.gov.eg</a>
Jordan	<a href="http://www.jfda.jo">http://www.jfda.jo</a>
Lebanon	<a href="http://cms1.omsar.gov.lb">http://cms1.omsar.gov.lb</a>
Morocco	<a href="http://srvweb.sante.gov.ma">http://srvweb.sante.gov.ma</a>
Oman	<a href="http://www.moh.gov.om">http://www.moh.gov.om</a>
Pakistan	<a href="http://www.dcomoh.gov.pk">http://www.dcomoh.gov.pk</a>
Qatar	<a href="http://www.nha.org.qa">http://www.nha.org.qa</a>
Saudi Arabia	<a href="http://www.sfda.gov.sa">http://www.sfda.gov.sa</a>
Sudan	<a href="http://www.nmpb.gov.sd">http://www.nmpb.gov.sd</a>
Tunisia	<a href="http://www.dpm.tn">http://www.dpm.tn</a>
United Arab Emirates	<a href="http://www.moh.gov.ae">http://www.moh.gov.ae</a>
Yemen	<a href="http://www.sbd-ye.org">http://www.sbd-ye.org</a>

*WHO Region for Europe*

Albania	<a href="http://www.qkkb.gov.al">http://www.qkkb.gov.al</a>
Andorra	<a href="http://www.salutibienestar.ad">http://www.salutibienestar.ad</a>
Armenia	<a href="http://www.pharm.am">http://www.pharm.am</a>
Austria	<a href="http://www.ages.at">http://www.ages.at</a>
Azerbaijan	<a href="http://www.pharm.az">http://www.pharm.az</a>
Belarus	<a href="http://www.rceth.by">http://www.rceth.by</a>
Belgium	<a href="http://www.fagg-afmps.be">http://www.fagg-afmps.be</a>
Bosnia and Herzegovina	<a href="http://www.alims.gov.ba">http://www.alims.gov.ba</a>
Bulgaria	<a href="http://www.bda.bg">http://www.bda.bg</a>
Croatia	<a href="http://www.almp.hr">http://www.almp.hr</a>
Cyprus	<a href="http://www.moh.gov.cy">http://www.moh.gov.cy</a>
Czech Republic	<a href="http://www.sukl.cz">http://www.sukl.cz</a>
Denmark	<a href="http://www.dkma.dk">http://www.dkma.dk</a>
European Medicines Agency	<a href="http://www.ema.europa.eu">http://www.ema.europa.eu</a>
Estonia	<a href="http://www.sam.ee">http://www.sam.ee</a>
Finland	<a href="http://www.nam.fi">http://www.nam.fi</a>
France	<a href="http://www.afssaps.fr">http://www.afssaps.fr</a>
Georgia	<a href="http://gdna.georgia.gov">http://gdna.georgia.gov</a>
Germany	<a href="http://www.bfarm.de">http://www.bfarm.de</a>

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**Medicines regulatory authority web sites (continued)**

Greece	<a href="http://www.eof.gr">http://www.eof.gr</a>
Hungary	<a href="http://www.ogyi.hu">http://www.ogyi.hu</a>
Iceland	<a href="http://www.imca.is">http://www.imca.is</a>
Ireland	<a href="http://www.imb.ie">http://www.imb.ie</a>
Israel	<a href="http://www.health.gov.il">http://www.health.gov.il</a>
Italy	<a href="http://www.aifa.gov.it">http://www.aifa.gov.it</a> & <a href="http://www.agenziafarmaco.it">http://www.agenziafarmaco.it</a>
Kazakhstan	<a href="http://www.dari.kz">http://www.dari.kz</a>
Kyrgyzstan	<a href="http://pharm.med.kg">http://pharm.med.kg</a>
Latvia	<a href="http://www.vza.gov.lv">http://www.vza.gov.lv</a>
Lithuania	<a href="http://www.vvkt.lt">http://www.vvkt.lt</a>
Luxembourg	<a href="http://www.ms.public.lu">http://www.ms.public.lu</a>
Malta	<a href="http://www.medicinesauthority.gov.mt">http://www.medicinesauthority.gov.mt</a>
Montenegro	<a href="http://sntcg.com">http://sntcg.com</a>
Netherlands	<a href="http://www.cbg-meb.nl">http://www.cbg-meb.nl</a>
Norway	<a href="http://www.legemiddelverket.no">http://www.legemiddelverket.no</a>
Poland	<a href="http://www.bip.urpl.gov.pl">http://www.bip.urpl.gov.pl</a>
Portugal	<a href="http://www.infarmed.pt">http://www.infarmed.pt</a>
Republic of Moldova	<a href="http://www.amed.md">http://www.amed.md</a>
Romania	<a href="http://www.anm.ro">http://www.anm.ro</a>
Russian Federation	<a href="http://www.roszdravnadzor.ru">http://www.roszdravnadzor.ru</a>
Serbia	<a href="http://www.alims.gov.rs">http://www.alims.gov.rs</a>
Slovakia	<a href="http://www.sukl.sk">http://www.sukl.sk</a>
Slovenia	<a href="http://www.jazmp.si">http://www.jazmp.si</a>
Spain	<a href="http://www.agemed.es">http://www.agemed.es</a>
Sweden	<a href="http://www.lakemedelsverket.se">http://www.lakemedelsverket.se</a>
Switzerland	<a href="http://www.swissmedic.ch">http://www.swissmedic.ch</a>
Tajikistan	<a href="http://health.tj">http://health.tj</a>
Turkey	<a href="http://www.iegm.gov.tr">http://www.iegm.gov.tr</a>
Ukraine	<a href="http://www.pharma-center.kiev.ua">http://www.pharma-center.kiev.ua</a>
United Kingdom	<a href="http://www.mhra.gov.uk/index.htm">http://www.mhra.gov.uk/index.htm</a>

*WHO Region for South-East Asia*

Bangladesh	<a href="http://www.ddabd.org">http://www.ddabd.org</a>
Bhutan	<a href="http://www.health.gov.bt/dra.php">http://www.health.gov.bt/dra.php</a>
India	<a href="http://cdsco.nic.in">http://cdsco.nic.in</a>
Indonesia	<a href="http://www.pom.go.id">http://www.pom.go.id</a>
Maldives	<a href="http://www.mfda.gov.mv">http://www.mfda.gov.mv</a>
Nepal	<a href="http://www.dda.gov.np">http://www.dda.gov.np</a>
Sri Lanka	<a href="http://www.health.gov.lk">http://www.health.gov.lk</a>
Thailand	<a href="http://www.fda.moph.go.th">http://www.fda.moph.go.th</a>

*WHO Region for the Western Pacific*

Australia	<a href="http://www.tga.gov.au">http://www.tga.gov.au</a>
Brunei Darussalam	<a href="http://www.moh.gov.bn">http://www.moh.gov.bn</a>
China	<a href="http://www.sfda.gov.cn">http://www.sfda.gov.cn</a>
Fiji	<a href="http://www.health.gov.fj">http://www.health.gov.fj</a>
Hong Kong SAR China	<a href="http://www.psdh.gov.hk">http://www.psdh.gov.hk</a>
Japan	<a href="http://www.pmda.go.jp">http://www.pmda.go.jp</a>
Malaysia	<a href="http://www.pharmacy.gov.my">http://www.pharmacy.gov.my</a>
Mongolia	<a href="http://www.moh.mn">http://www.moh.mn</a>
New Zealand	<a href="http://www.medsafe.govt.nz">http://www.medsafe.govt.nz</a>
Philippines	<a href="http://www.bfad.gov.ph">http://www.bfad.gov.ph</a>
Republic of Korea	<a href="http://ezdrug.kfda.go.kr">http://ezdrug.kfda.go.kr</a>
Singapore	<a href="http://www.hsa.gov.sg">http://www.hsa.gov.sg</a>
Vietnam	<a href="http://www.dav.gov.vn">http://www.dav.gov.vn</a>

# Essential Medicines

## Regulatory action needed to stop the sale of oral artemisinin-based monotherapy

Continued use of oral artemisinin-based monotherapy is widely considered as one of the main contributing factors to the development and spread of resistance to artemisinin and its derivatives. Few patients take the full seven-day course of monotherapy required to achieve high cure rates — most patients tend to discontinue treatment after two or three days due to the rapid resolution of symptoms provided by artemisinin. This results in persistent parasitaemia exposed to sub-therapeutic drug levels. In 2007, the World Health Assembly adopted a resolution to progressively remove oral artemisinin-based monotherapy from the market and instead deploy artemisinin-based combination therapies (ACTs) for the treatment of uncomplicated falciparum malaria. While 34 countries have withdrawn marketing authorization for oral artemisinin-based monotherapy, 29 countries have not yet taken regulatory action. Out of 73 companies involved in the production and marketing of these medicines, a total of 36 companies have de-listed oral artemisinin-based monotherapy from their product catalogues but 37 companies — mainly those targeting the private sector markets of malaria-endemic countries — are still actively providing monotherapy in this sector. Progress made by regulatory authorities at country level shows that phasing out oral artemisinin-based monotherapy from the market is possible through a range of interventions as long as government commitment and strong stewardship of the national regulatory authorities is maintained.

### Artemisinin-based monotherapy and risk of *Plasmodium falciparum* drug resistance

Malaria causes an estimated 243 million clinical attacks every year with 863 000 deaths, mostly in children under 5 years of age, due to *Plasmodium falciparum* (1). WHO recommends artemisinin-based combination therapies (ACTs) as the mainstay of treatment of uncomplicated *P. falciparum* malaria (2). The rationale of combining a rapidly acting artemisinin

derivative with a second longer acting antimalarial partner — killing the parasite using two different modes of action — is to delay the development of resistance. Prevention of artemisinin resistance is particularly important as there are no alternative antimalarial medicines under development with equivalent levels of efficacy expected to become available over the next 7–8 years (3).

Artemisinin and its derivatives are highly efficacious. They rapidly eliminate asexual parasite stages and early sexual forms of falciparum malaria, producing a rapid clinical and parasitological response (4). When used as monotherapy, artemisinin derivatives need to be given for seven days to achieve high cure rates, while three-day monotherapy treatment

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results in unacceptably high (48–54%) recrudescence rates (5). Consequently, there are two main product presentations which promote artemisinin resistance:

- Medicinal products with 5–7 day administration of artemisinin-based monotherapy.
- ACTs which are co-blistered rather than co-formulated.

Full seven-day treatment is impractical and most patients tend to discontinue treatment early due to the rapid clinical resolution provided by artemisinin. With co-blistered ACTs many patients tend to take the three-day treatment of the artemisinin derivative and discard the partner medicine (e.g. amodiaquine or mefloquine) due to the poor tolerability of the latter medicines. Both products, which lead to inadequately dosed artemisinin monotherapy, leave the parasite exposed to sub-therapeutic blood levels of the medicine which promotes the development of parasite resistance by eliminating the most sensitive parasite strains and leaving the more resistant ones to multiply unrestrained.

### **Emergence and selection of drug resistant parasites**

The emergence of resistance to antimalarial medicines is initiated by rare spontaneous mutations which provide survival advantages to the parasite while exposed to a specific antimalarial compound. When exposed to the medicine in question (drug pressure), the mutant parasite strains which have a survival advantage get selected in favour of the sensitive ones. Mutations can originate in the population of parasites from the same geographical area or in parasites from different areas. Migrating populations contribute to the development and spread of resistance by importing mutated parasites from other geographical areas which then recombine with the local

parasites to give rise to a pool of mutated and recombined parasites. Antimalarial immunity in patients, which increases in proportion to the intensity of malaria transmission, might conceal the effects of drug resistance and delay the detection of drug resistant infections (6).

*Plasmodium falciparum* has thus far developed resistance to all classes of antimalarial medicines used in its treatment (6). While quinine remained effective for decades after its large-scale introduction in the early 20<sup>th</sup> century, the development of resistance to the other antimalarial compounds emerged relatively faster, varying from 12 years for chloroquine to five years for mefloquine, to approximately one year for proguanil, sulfadoxine-pyrimethamine and atovaquone. In the 1950s and 1960s, *P. falciparum* resistance to chloroquine and sulfadoxine-pyrimethamine was first detected in the Pailin province, Western Cambodia (4), from where it subsequently spread to the Indian subcontinent in the 1970s and then to East African countries in the 1980s.

More recently in 2009, scientists confirmed the first cases of falciparum resistance to artemisinin derivatives in the same province of Pailin (8). In this area artemisinins have been extensively used as monotherapy over the past decade, and this may have contributed to the development of resistance together with other unidentified factors (4, 8). There is major concern that artemisinin resistance in *P. falciparum* malaria parasites may increase and spread to other areas of the world.

The loss of artemisinin derivatives will have devastating consequences on people's health in malaria-endemic countries and threaten recent malaria control progress achieved in many countries.

### **Drug pressure and its impact on antimalarial drug resistance**

Past experience shows that once resistance has arisen the removal of drug pressure can prolong the useful therapeutic life of the corresponding medicine (9). Mutations associated with drug resistance in *P. falciparum* generally affect the parasite's fitness. Studies undertaken with chloroquine and mefloquine showed that parasite susceptibility to the corresponding active pharmaceutical ingredient was restored after discontinuing use of the medicines.

In China, in vivo resistance to chloroquine decreased over a 5–8 year period from more than 84% to 40%. In certain regions of Malawi — the first African country to discontinue chloroquine use in 1993 in favour of sulfadoxine-pyrimethamine — molecular markers of chloroquine resistant parasites decreased in prevalence over time (9). For other antimalarial medicines, such as sulfadoxine-pyrimethamine, drug resistant mutations may persist after drug pressure is removed if they do not affect the parasite's fitness or if secondary mutations occur, providing compensatory mechanisms to strengthen parasite fitness.

### **Phasing out oral artemisinin-based monotherapy**

Based on the biological mechanisms of resistance observed with the other antimalarial compounds, it is expected that with removal of oral artemisinin-based monotherapy the resistance of *P. falciparum* to artemisinins will either reduce or stabilize at prevailing levels rather than get worse. Both mechanisms will result in extending the useful therapeutic life of artemisinin derivatives. WHO therefore urges Member States to cease the marketing and use of oral artemisinin-based monotherapy in both the public and private sectors and to promote the use of artemisinin-based combination therapies. As part of World Health Assembly Resolution WHA60.18 (10), these

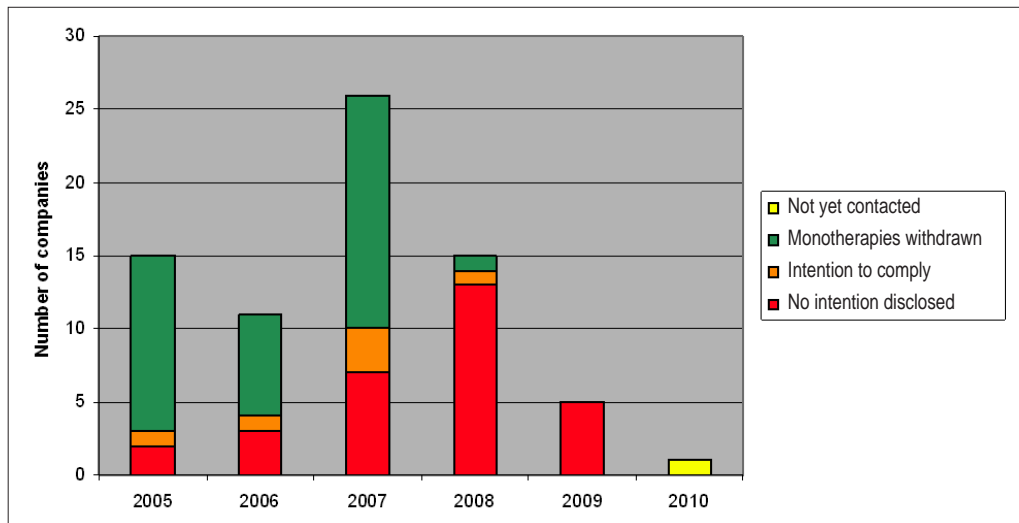
recommendations were endorsed by all WHO Member States in May 2007. Since 2006, the WHO Global Malaria Programme has contacted the major procurement and funding agencies in relation to these recommendations and, as a result, all major agencies have progressively discontinued funding or procurement of these medicines.

### **Monitoring the phasing out of artemisinin-based monotherapy**

Until all ACTs become available as fixed-dose combinations, oral artemisinin-based monotherapies will need to be manufactured for co-blistering with partner medicines; the call is against the sale and use of oral artemisinin-based monotherapy. To track compliance with Resolution WHA60.18 by pharmaceutical companies marketing these medicines and progress in implementation of regulatory action by national drug regulatory authorities, WHO has established a web-based monitoring system. Regularly updated information can be accessed through the following links: [http://www.who.int/malaria/monotherapy\\_manufacturers.pdf](http://www.who.int/malaria/monotherapy_manufacturers.pdf) (pharmaceutical companies) and [http://www.who.int/malaria/monotherapy\\_NDRAs.pdf](http://www.who.int/malaria/monotherapy_NDRAs.pdf) (national drug regulatory authorities).

Since 2005, WHO has identified a total of 73 pharmaceutical companies involved in the production and marketing of oral artemisinin-based monotherapy medicines. On a regular basis, WHO contacts these companies in order to update their positions with regard to WHO recommendations. All but one of the 36 companies which have ceased marketing so far have been identified in the period from 2005–2007; action was taken following repeated requests from WHO. Companies identified more recently are less prone to withdraw their products from the market. By April 2010, an additional six companies had declared their intentions to comply, but have not taken action so far and a total of 30 companies have not

**Figure 1. Companies marketing oral artemisinin-based monotherapies by year of identification by WHO updated on a regular basis (last update 13 April 2010)**



disclosed their position (Figure 1). Nearly all companies which have a consistent market share in public sector procurement funded by international agencies have de-listed oral artemisinin-based monotherapy medicines from their product catalogues. However, smaller companies mainly targeting private sector markets are more prone to ignore the WHO appeal. When responsible companies comply with WHO recommendations and withdraw their monotherapy products, they leave 'niche markets' which are rapidly exploited by opportunistic companies manufacturing monotherapy and substandard products. Most of the companies still involved in the marketing of oral artemisinin-based monotherapy medicines are located in India (21), followed by Nigeria (5), Kenya (2) and Viet Nam (2), as well as the Democratic Republic of Congo, Dubai (United Arab Emirates), Ghana, Greece, Netherlands, Pakistan and Switzerland (1 company each).

One of the main reasons for the limited success in phasing out oral artemisinin-

based monotherapy is the poor regulation of pharmaceutical markets in malaria-endemic countries. In February 2010, out of the 78 national regulatory authorities (NRAs) of falciparum-endemic countries, 49 have either never registered or have taken regulatory measures to withdraw marketing authorizations of oral artemisinin-based monotherapy and 29 still do not yet comply with WHO recommendations. Most of the countries which have not yet taken regulatory steps are located in the WHO African Region (16 NRAs) followed by the South-East Asia Region (6 NRAs) and the Western Pacific Region (3 NRAs).

The regulation of pharmaceutical markets in malaria-endemic countries is a complex process. A number of successful examples show that phasing out oral artemisinin-based monotherapy can succeed. Countries are adopting WHO recommendations to progressively phase out artemisinin-based monotherapies and adapt them to their national context. In some countries, like Cameroon and Côte d'Ivoire, the new regulations aim to align

the availability of products for sale in the private sector with those listed in the national treatment guidelines and available in the public sector. Other countries like Benin have used this opportunity not only to remove oral artemisinin-based monotherapy but also all formulations of chloroquine, which is no longer effective due to high levels of *P. falciparum* resistance. The critical step in Benin was to ensure large-scale availability of ACTs. For some countries, e.g. China and Viet Nam, the main target of decisions of the national health authorities has been the removal of oral artemisinin-based monotherapy from the public sector, following change of the national treatment guidelines. The examples of India and Pakistan show the importance of national regulatory authorities in coordinating this initiative and support provided by the national Malaria Control Programme and WHO in both countries to accelerate the process. The active recall of existing stocks of chloroquine and sulfadoxine-pyrimethamine in Burundi has proven to be highly effective.

### **The way forward: targets and timelines for action**

The active withdrawal of a medicine from the market in the interest of public health through a regulatory approach — in this particular case to limit the risk of development of resistance — is unprecedented. Many steps are involved in the manufacture of artemisinin-based medicines, from the planting of the seeds to extraction of the active pharmaceutical ingredient (API) and subsequent manufacture of the finished pharmaceutical products (FPPs). Thereafter the sale of oral artemisinin-based monotherapy takes place in the context of domestic and international market dynamics. A variety of interventions can and have successfully been applied at these various steps in order to interrupt both the manufacture and sale of these monotherapies. Thus, measures

affecting both international and domestic markets, and targeting both APIs and FPPs can be applied to phase out oral artemisinin-based monotherapy medicines from the markets.

Export markets can be influenced by regulatory actions targeting those countries which are the major exporters of these medicines. In particular, withdrawing manufacturing and export licenses for FPPs can prevent pharmaceutical companies from exporting their monotherapy products to malaria-endemic countries. To protect domestic markets, the most effective strategy is to stop import licences and not to grant marketing authorizations for such products. Domestic manufacturers should be regulated more stringently with regard to import licenses for APIs, e.g., not granting API import licenses to companies exclusively manufacturing oral artemisinin-based monotherapies. In addition, to regulate domestic companies involved in the re-packaging or re-branding of artemisinin-based FPPs produced in other countries, FPP import licenses should be suspended for companies exclusively marketing oral artemisinin-based monotherapies.

It is crucial to ensure large-scale availability of ACTs in both the public and private sectors, before oral artemisinin-based monotherapies can effectively be removed from the market. Based on the initial experiences of successful countries, Table 1 overleaf offers generic timelines for progressively removing these medicines from the market which can be adapted to specific situations.

### **Conclusion**

Progress made by several pharmaceutical companies and regulatory authorities at country level show that phasing out oral artemisinin-based monotherapy medicines from the markets is possible through a range of interventions. However, the problem is still rife and is cur-

**Table 1. Generic guide with timelines to phase out oral artemisinin-based monotherapy medicines from the market**

Action	Task	Timeline
Step 1	Agreement on timeframe of phasing out oral artemisinin-based monotherapies in synchrony with large-scale implementation of artemisinin-based combination therapies (ACTs)	Immediate
Step 2	Suspension of new approvals of marketing authorizations for oral artemisinin-based monotherapies	Immediate
Step 3	Suspension of import licences for artemisinin or its derivatives (as API or FPP) to domestic companies exclusively marketing oral artemisinin-based monotherapies	3–4 months
Step 4	Large-scale deployment of ACTs in the public sector and communication to prescribers and consumers to move away from monotherapies	Time X*
Step 5	Widespread availability and affordability of ACTs in the private sector	Time Z**
Step 6	Withdrawal of marketing authorization and of manufacturing licences for oral artemisinin-based monotherapies as FPPs	6 months after time X
Step 7	Suspension of export licence for oral artemisinin-based monotherapies as FPPs	6 months after time X
Step 8	Complete elimination of oral artemisinin-based monotherapy medicines as FPPs from the market	10–12 months after time X
Step 9	Active recall of oral artemisinin-monotherapies from the market	3 months after time Z

\* X refers to the time at which a country will deploy on a large scale artemisinin-based combination therapies in the public sector, generally associated with external funding for procurement (e.g. from GFATM or other sources). All subsequent timelines are conditioned on this.

\*\* Z requires distribution of quality ACTs at subsidized prices in the private sector, as expected in countries participating in the Affordable Medicines Facility – malaria (Global Fund to Fight AIDS, Tuberculosis and Malaria [GFATM]).

rently one of the major threats for development of drug resistance. The response of pharmaceutical companies to stop marketing oral artemisinin-based monotherapies has been successful in those with a consistent market share in

accessing international funds for public sector procurement. Smaller companies which mainly target the pharmaceutical private sector in developing countries have largely compromised the success of this approach. Thus, ultimate success in

phasing out oral artemisinin-based monotherapy depends on effective drug regulation at country level. Only the removal of marketing authorizations for oral artemisinin-based monotherapies will make them unavailable in the public and formal private sectors. A flourishing informal private sector, which is common in many malaria-endemic countries, will still continue to provide oral monotherapy to potential users and can be overcome by the provision of good access to quality medicines through a national drug supply management system.

Experience shows that a number of critical steps should be taken in the process of phasing out oral artemisinin-based monotherapy from the market. It is essential to synchronize these with the large-scale deployment of ACTs in the public sector and the provision of reasonable timelines allowing the progressive adaptation and response of the private sector to new health directives.

Enhanced action to phase out oral artemisinin-based monotherapy medicines in the remaining malaria-endemic countries is urgently required. Government commitment and strong stewardship of national regulatory authorities is required to achieve this. Artemisinin resistance — which is being accelerated by the use of oral artemisinin-based monotherapy — is too grave a public health risk to continue deployment of these medicines..

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# Safety and Efficacy Issues

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## Leflunomide and peripheral neuropathy

**Canada** — Neuropathy has been reported in association with several disease-modifying antirheumatic drugs. During the past seven years, additional data regarding the suspected association between peripheral neuropathy and leflunomide have emerged in the medical literature.

Leflunomide is a disease-modifying antirheumatic drug (DMARD) indicated for use in adults with active rheumatoid arthritis (1). It has been marketed in Canada since 2000 under the brand name Arava® and is also available in generic form.

Peripheral neuropathy is an impairment of the peripheral motor, sensory or autonomic nervous system (2). Signs and symptoms include muscular weakness or flaccid paralysis and sensory disturbances, including pain (2). Neuropathy has been reported in association with several DMARDs, including sulfasalazine, chloroquine and penicillamine (3, 4). Over the last seven years, several cases of peripheral neuropathy suspected of being associated with leflunomide have been published (5–15). Patients had paraesthesia or weakness, or both, in the upper or lower extremities, or both. In a few cases the symptoms were severe or debilitating (12–16). The incidence of peripheral neuropathy has ranged from 1.4% to 10% in open studies to assess leflunomide neurotoxicity (5–8). In these studies, the proportion of patients for whom this adverse reaction (AR) improved after discontinuation of the drug or reduction of the dosage ranged from 37% to 100%.

*Extracted from Canadian Adverse Reaction Newsletter, Volume 20, Number 2, 2010 at [http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcej\\_v20n2-eng.php](http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcej_v20n2-eng.php)*

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### Saquinavir mesylate: prolongation of QT and PR intervals

**Canada** — Healthcare professionals have been informed of important new safety information regarding the use of saquinavir mesylate (Invirase®) and significant dose-dependent prolongation of QT and PR intervals in healthy volunteers.

Saquinavir is authorized for the treatment of HIV-1 infected adult patients and should only be given in combination with ritonavir and other antiretroviral medicinal products.

Based on the findings of a dedicated electrocardiogram study with saquinavir/ritonavir in healthy volunteers, dose-dependent prolongation of QT and PR intervals have been observed in healthy volunteers receiving ritonavir-boosted saquinavir.

Saquinavir/ritonavir should not be used in patients already taking medications known to cause QT interval prolongation or in patients with a history of QT interval prolongation.

Caution is warranted when administering ritonavir-boosted saquinavir to patients with pre-existing conduction system disease.

**Reference:** Communication dated 14 April 2010 from Hoffmann-La Roche Limited at <http://www.hc-sc.gc.ca>.

### Human immune globulin: intravascular haemolysis

**Canada** — Healthcare professionals have been informed of changes to the prescribing information, including new contraindications and conditions for use, for the treatment of immune thrombocytopenic purpura (ITP) with human Rho(D) immune globulin (WinRho® SDF). There have been rare serious (sometimes fatal) adverse events of intravascular haemolysis (IVH) and its complications which have been reported following ITP treatment with WinRho® SDF.

WinRho® SDF should not be administered to patients:

- with ITP secondary to other conditions including leukaemia, lymphoma, or active viral infections with EBV (Epstein-Barr virus) or HCV (hepatitis C)
- who are elderly with co-morbidity predisposing to acute haemolytic reaction (AHR) or its complications
- with evidence of autoimmune haemolytic anaemia (Evan Syndrome), or Systemic Lupus Erythematosus (SLE) or anti phospholipid antibody syndrome (APS)
- who are IgA deficient.

Patients treated with WinRho® SDF for ITP should be closely monitored in a healthcare setting for at least eight hours after administration. Urine dipstick testing for blood should be conducted before dosing and at 2, 4 and 8 hours after receiving the dose.

In post-marketing surveillance from March 1995 to March 2009 the manufacturer reported a total of 180 serious case reports of suspected and/or confirmed cases of IVH worldwide. A disproportionate number of IVH cases have been reported in patients with ITP secondary to haematological malignancies such as leukaemia or lymphoma, or active viral infections with HCV and EBV.

**Reference:** Communication dated 22 March 2010 from Cangene Corporation at <http://www.hc-sc.gc.ca/>.

## **Irinotecan-induced severe neutropenia: UGT1A1 variant alleles**

**Singapore** — Irinotecan is converted in the body to a metabolite called SN-38, which is 100 to 1000 times more potent than irinotecan itself. SN-38 is inactivated primarily by UGT1A1 which glucuronidates SN-38 to an inactive metabolite, SN-38G. UGT1A1 is the same enzyme that mediates bilirubin conjugation. Glucuronidating activity is reduced when variants of the UGT1A1 gene, UGT1A1\*28 or UGT1A1\*6 are present. UGT1A1\*28 contains seven, rather than six, thymine-adenine (TA) repeats in the UGT1A1 promoter region and reduces enzyme expression; UGT1A1\*6 represents a nucleotide change from guanine (G) to adenine (A) that causes an amino acid change from glycine to arginine and lowers the enzyme's activity. As a result, patients with these variants have higher blood levels of SN-38 after receiving the same dose of irinotecan.

Polymorphisms in other UGT genes as well as ABCB1, ABCG2, ABCC2 and SLCO1B1 genes which encode proteins involved in irinotecan transport, may also contribute to variation in irinotecan and SN-38 pharmacokinetics and severity of neutropenia, but the evidence is considerably less well developed than for UGT1A1\*6 and \*28. No definitive clinical studies have been published yet on the impact of irinotecan dosage adjustment on response rate based on a patient's genotype. This is an active area of clinical research internationally.

In 2005, the United States Food and Drug Administration (FDA) amended the product label for Camptosar®, a brand of irinotecan used in the US, to warn of an increased risk of severe neutropenia among patients who are homozygous for UGT1A1\*28. This decision was reached after reviewing data from several clinical trials that supported the conclusion of a greater risk of Grade 3 or 4 neutropenia in patients homozygous for UGT1A1\*28. Another meta-analysis of nine studies (821 subjects) from North America and Europe, published in 2007, confirmed a significant association between UGT1A1\*28 genotype and severe neutropenia at doses greater than 150 mg/m<sup>2</sup>, but no association was seen at lower doses (100–125 mg/m<sup>2</sup>). In 2008, a clinical study from Taiwan demonstrated that patients who were either heterozygous or homozygous for UGT1A1\*28 had a higher rate of neutropenic fever and grade 3 or 4 neutropenia.

In Japan, the Pharmaceutical and Medical Devices Agency (PMDA) also examined the evidence for an association between UGT1A1 variants and neutropenia. The UGT1A1\*28 variant is much less common in Japanese compared to Caucasians. On the other hand, UGT1A1\*6 is not uncommon in Japanese, yet is absent in Caucasians. In

2008, PMDA updated its product label for irinotecan to alert prescribers of the association between increased risk of serious adverse events and UGT1A1\*6 and \*28 variants.

### Local Context

The Health Sciences Authority (HSA) has reviewed the distribution of UGT1A1 variants in the three major ethnic groups of Singapore — Chinese, Malay, and Indian using data from the National Cancer Centre (16,17), the National University Hospital (18), and the Singapore Genome Variation Project (19). Among Singapore Indians, the genotype distribution of the UGT1A1\*28 variant is comparable to Caucasians, while among Singapore Chinese, the genotype distribution of the UGT1A1\*6 variant is similar to Japanese. The prevalence of double heterozygotes (\*6/\*28) in Singapore is 6.9%, 1.2% and 2.9% in Chinese, Malays and Indians, respectively.

In view of the available evidence of greater risk of irinotecan toxicity associated with UGT1A1\*6 and UGT1A1\*28 variants and its potential impact on our local population, the HSA Pharmacogenetics Advisory Committee has advised that the package inserts for irinotecan be updated. A genotyping test for UGT1A1\*6 and UGT1A1\*28 variants is available at the National Cancer Centre.

The era of genomics is producing an abundance of information about genetic variation within and across populations. As studies gradually dissect the information and establish linkages between genetic variations and response to drugs, they add to a body of knowledge that will help physicians tailor therapies for the individual characteristics of their patients.

**Reference:** Health Sciences Authority, 19 April 2010 at <http://www.hsa.gov.sg>

## Combination of niacin/ laropiprant and simvastatin: myopathy

**Singapore** — The Health Sciences Authority (HSA) has recently been informed of the results of an interim analysis from an ongoing study, HPS2-THRIVE, which suggest a higher incidence of myopathy observed in Chinese patients on concomitant extended release (ER) niacin/laropiprant 2 g/40 mg (Tredaptive®) and simvastatin 40 mg (with or without ezetimibe).

ER niacin/laropiprant is a lipid-lowering agent indicated for the treatment of dyslipidaemia. It contains a combination of ER niacin, a lipid-modifying agent and laropiprant, a potent, selective antagonist of the prostaglandin D2 (PGD2) receptor subtype 1 (DP1). Laropiprant is a novel agent that is added to the combination to suppress the PGD2 mediated flushing that is associated with the use of niacin. Tredaptive® has been licensed for use in Singapore since March 2009.

Myopathy and rhabdomyolysis are known adverse effects of HMG-CoA reductase inhibitors (statins), and the risk increases with higher doses and concomitant use of certain CYP3A4 inhibitors such as gemfibrozil and ciclosporin (1).

HPS2-THRIVE is a double blind, randomized placebo controlled study to assess the long term clinical effects of increasing HDL-cholesterol with ER niacin/laropiprant in 25 000 patients with pre-existing atherosclerotic vascular disease who were receiving simvastatin 40 mg daily (plus ezetimibe 10 mg daily, where indicated). This study, sponsored by Oxford University, is currently conducted in China, Scandinavia and United Kingdom. The study is currently in progress and is expected to be completed in 2012.

HSA has not received any local reports of rhabdomyolysis or myopathy associated with Tredaptive® or in combination with statins to date. Physicians prescribing the combined therapy of Tredaptive® with statins are advised to carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and when dosage of either drug is increased.

**Reference:** Health Sciences Authority, 19 April 2010 at <http://www.hsa.gov.sg>

## Entacapone/carbidopa/levodopa: prostate cancer

**United States of America** —The Food and Drug Administration (FDA) is evaluating clinical trial data that may suggest that patients taking Entacapone/carbidopa/levodopa (Stalevo®), a Parkinson disease medication, may be at increased risk for developing prostate cancer. At this time, FDA's review of Stalevo® is ongoing and no new conclusions or recommendations about the use of this drug have been made.

Entacapone is also available as a single-ingredient product sold under the brand name Comtan®. Both Stalevo® and Comtan® are used to treat symptoms of Parkinson disease.

The data being reviewed are from a long-term clinical trial called Stalevo® Reduction in Dyskinesia Evaluation – Parkinson's Disease (STRIDE-PD). STRIDE-PD evaluated the time to onset of dyskinesia (difficulty controlling voluntary movement) in patients with Parkinson disease taking Stalevo compared to those taking only carbidopa/levodopa. An unexpected finding in the trial was that a greater number of patients taking Stalevo® were observed to have prostate cancer com-

pared to those taking carbidopa/levodopa.

**Reference:** FDA Safety Announcement dated 31 March 2010 at <http://www.fda.gov>

## Becaplermin contraindicated in cancer patients

**European Union** — Following a review of the available data on a possible risk of cancer in patients using becaplermin (Regranex®), the European Medicines Agency has concluded that the medicine must not be used in patients who have any form of cancer. A similar restriction previously applied but only for patients who had a skin cancer close to the area where the gel was to be applied.

Regranex® is a gel that is used together with other wound care measures to treat long-term skin ulcers in people with diabetes.

The review, conducted by the Agency's Committee for Medicinal Products for Human Use (CHMP), was initiated at the request of the European Commission because of reports of cancer developing in a small number of patients using the gel. The Committee noted that while there was no firm evidence of a link between Regranex® and cancer there was also not enough evidence to rule out such a link.

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## **Panitumumab: hypersensitivity reactions**

**United Kingdom** — Healthcare professionals have been informed of new reports of serious hypersensitivity reactions, including anaphylaxis, in patients receiving panitumumab (Vectibix®), some of which have been fatal. Panitumumab is associated with mild to moderate infusion-related reactions, including chills, dyspnoea, flushing, hypertension, hypotension, pyrexia, tachycardia and vomiting in about 3% of patients. However, severe infusion reactions, including anaphylaxis, angioedema, bronchospasm, cardio-respiratory arrest and hypotension requiring treatment may occur and are potentially life-threatening.

The product Information has been updated to highlight the following:

- Panitumumab is contraindicated in patients with a history of severe or life threatening hypersensitivity reactions to panitumumab;
- Serious infusion-related reactions are unpredictable and can occur suddenly. Panitumumab should be permanently discontinued if a severe or life threatening reaction occurs.
- In patients experiencing a mild or moderate infusion-related reaction, the infusion rate should be reduced for the duration of that infusion. It is recommended to maintain this lower rate in all subsequent infusions.

Hypersensitivity reactions occurring more than 24 hours after infusion have also been reported. Patients should be warned of the possibility of a late onset reaction and instructed to contact their physician if symptoms of a hypersensitivity reaction occur.

**Reference:** Communication from the manufacturer dated 16 April 2010. Healthcare Products Regulatory Agency (MHRA) at <http://www.mhra.gov.uk>

# Regulatory Action and News

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## Ceftobiprole medocaril: discontinuation of sale

**Canada** — The manufacturer of ceftobiprole medocaril for injection (Zeftera®) is discontinuing sale as of 16 April 2010.

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*.

This action is being taken by the manufacturer in response to recent regulatory recommendations in the United States and European Union to not approve Zeftera® for this indication due to concerns regarding the conduct of clinical trials.

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 dated 9 April 2010 from Janssen-Ortho Inc. at <http://www.hc-sc.gc.ca>

## Bufexamac : revocation of marketing authorization

**European Union** — The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has recommended that market-

ing authorizations for bufexamac-containing medicines be revoked.

The CHMP recommendations follow a scientific review which identified a high risk of sometimes serious contact allergic reactions with bufexamac. The risk was even higher in patients with pre-disposing conditions such as certain forms of eczema for which bufexamac is frequently prescribed. Furthermore, the allergic reactions caused by bufexamac are very similar to the disease being treated which may lead to a potential delay in the correct diagnosis and treatment of patients. It is also likely that the difficulty to differentiate between a treatment failure and an allergic reaction has led to the cases of contact allergic reaction being underreported. In addition to this, the data to support the effectiveness of bufexamac are very limited.

Bufexamac is a nonsteroidal anti-inflammatory drug (NSAID) used in topical formulations to treat dermatological diseases (eczema and dermatitis) and proctological conditions (haemorrhoids and anal fissure). Bufexamac-containing medicines have been available in EU Member States since the 1970s.

**Reference:** Press Release dated 22 April 2010. EMA/246395/2010 at <http://www.ema.europa.eu>

## Rosiglitazone: authorization suspended

**Saudi Arabia** — The Saudi Food and Drug Authority (SFDA) has reviewed the safety of rosiglitazone (Avandia®) which is used in the treatment of type 2 diabetes mellitus. Based on growing evidence from

clinical trial meta-analyses and observational studies indicating serious cardiovascular adverse events associated with the use of rosiglitazone, the Advisory Committee for Pharmacovigilance in Saudi Arabia has concluded that:

- The risk of using rosiglitazone outweighs its benefit, in particular with regard to cardiovascular events including myocardial infarction and congestive heart failure, and increased risk of fractures.
- Safer alternatives which could be used for treatment of diabetes mellitus are available in Saudi Arabia.

Consequently, the Committee for Medicinal Products Registration decided to suspend marketing authorization for a period of six months during which the manufacturer has the opportunity to provide the SFDA with evidence as to why rosiglitazone and combination products containing rosiglitazone should not be permanently removed from the Saudi Arabian market. Rosiglitazone containing products marketed in Saudi Arabia include Avandia®, Avandamet® and Avandaryl®

**Reference:** Saudi Food and Drug Authority Advisory, 17 March 2010 <http://dpic.sfda.gov.sa>

### **Sitimagene ceradenovec: withdrawal of marketing authorization application**

**European Union** — The European Medicines Agency has been formally notified by the manufacturer of its decision to withdraw its application for a centralized marketing authorization for the advanced therapy medicinal product sitimagene ceradenovec (Cerepro®).

Cerepro received an orphan designation on 6 February 2002 and was intended for the treatment of patients with high-grade

operable glioma. The company has been unable to demonstrate to the Committee that its main study provides clear evidence of a clinically meaningful benefit in relation to risk.

**Reference:** Press Release dated 11 March 2010. EMA/151854/2010 at <http://www.ema.europa.eu>

### **Albinterferon alfa-2b: withdrawal of marketing authorization application**

**European Union** — The European Medicines Agency has been formally notified by the manufacturer of its decision to withdraw its application for a centralized marketing authorization for the medicine albinterferon alfa-2b (Joulferon®), 900 mg powder and solvent for solution for injection in pre-filled pen and vials.

This medicine was intended to be used in combination with ribavirin for the treatment of adults with chronic hepatitis C virus infection who have compensated liver disease and have not been previously treated with interferon alfa.

The decision to withdraw the application was based on preliminary comments of Committee for Medicinal Products for Human Use (CHMP) that additional new data would be requested for a favourable opinion. These could not be generated within the timeframe allowed in the centralized procedure.

**Reference:** Press Release dated 19 April 2010. EMA/249301/2010 at <http://www.ema.europa.eu>

### **Docetaxel: withdrawal of marketing authorization application**

**European Union** — The European Medicines Agency has been formally notified by the manufacturer of its decision to withdraw its application for a

centralized marketing authorization for the medicinal product docetaxel (docetaxel Mylan®), 10 mg/ml powder and solvent for solution for infusion.

The medicine was developed as a generic to be used for breast cancer, non small cell lung cancer, prostate cancer, gastric adenocarcinoma and head and neck cancer.

The application was withdrawn because the Committee for Medicinal Products for Human Use (CHMP) considers that the data provided do not allow it to conclude on a positive benefit-risk balance.

**Reference:** Press Release dated 15 March 2010. EMA/164498/2010 at <http://www.ema.europa.eu>

## **Rotarix® oral vaccine: new information**

**European Union** — The European Medicines Agency is aware of new information reported by the manufacturer of Rotarix® relating to the unexpected presence of DNA of a non-disease causing viral strain in batches of the oral vaccine. Through its own tests, the company has confirmed the finding of DNA originating from porcine circovirus type 1. This virus is commonly found in certain meat and other food products, and is not known to cause disease in either animals or humans.

An initial review by the Agency's Committee for Medicinal Products for Human Use (CHMP) considered these findings on 17 March 2010 and concluded that no action was necessary at this point. The Committee stresses that the findings do not present a public health threat. It also noted that there have been no safety signals reported with the vaccine that suggest otherwise.

It is nonetheless clear that viral DNA should not be present in the vaccine and

that its source is unclear. The Committee has therefore requested the manufacturer to provide further information as a matter of urgency.

**Reference:** Press Release dated 22 March 2010. EMA/189350/2010 at <http://www.ema.europa.eu>

## **Paediatric Medicines Regulators Network**

**World Health Organization** — Only a limited number of medicines that are currently available have been clinically evaluated for their safety and efficacy in the paediatric population. The lack of suitable paediatric medicines, combined with an inconsistent regulatory framework poses significant challenges in ensuring access to medicines for a particularly vulnerable patient population. There is thus a significant need for research and development on paediatric medicines, biological products and vaccines.

Following recommendations made at the 13th International Conference of Drug Regulatory Authorities (ICDRA) in 2008, and as part of the World Health Organization's Better Medicines for Children initiative, a Paediatric Medicines Regulators Network (PMRN) has been established by national medicines regulatory authorities. The first meeting of the PMRN was held at WHO, Geneva, in February 2010.

The objectives of the meeting were to:

- Define PMRN structure, aims and potential role in the development of international recommendations on paediatric medicines.
- To review the current regulatory, scientific and ethical standards for paediatric medicines and to determine their applicability to developing country settings.

Background documents concerning clinical trials, ethics and international guidelines on research in the paediatric population formed the basis for discussion. During the meeting, the following topics were considered:

- Common standards for registration of paediatric medicines.
- Mechanisms for information sharing between national medicines regulatory authorities.
- Training and capacity development in developing countries (e.g., IT infrastructure, expertise in the review of clinical trials and marketing applications).

As a first step, participants agreed to:

1. Support establishment of the PMRN.
2. Promote effective communication mechanisms.
3. Work with WHO in assisting national medicines regulatory authorities worldwide on matters concerning regulation of paediatric medicines.

In addition, there was agreement on the need for capacity building for effective regulation of medicines for children. WHO will provide the PMRN Secretariat. Interested national medicines regulatory authorities are welcome to participate in the PMRN.

The objectives of the PMRN are to:

- Provide a forum for discussion.
- Build awareness on paediatric medicines regulatory considerations and work towards consensus on regulatory standards for paediatric medicines.
- Promote capacity for development and formulation of paediatric medicines.
- Support appropriate conduct of paediatric clinical trials, including establishing links with existing networks. Facilitate scientific and ethical review of clinical trials for the development of paediatric medicines.
- Strengthen licensing (approval) systems for paediatric medicines.
- Promote evidence-based recommendations and advice on all aspects of medicines for children, including dosage forms, excipients and delivery devices.
- Provide a forum for promoting paediatric pharmacovigilance.
- Collaborate with other networks and nongovernmental organizations.

**References:** [http://www.who.int/childmedicines/paediatric\\_regulators/meetings/en/index.html](http://www.who.int/childmedicines/paediatric_regulators/meetings/en/index.html)

# Consultation Document

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## The International Pharmacopoeia

### Emtricitabini et tenofovir compressi Emtricitabine and tenofovir tablets

Draft proposal for *The International Pharmacopoeia* (March 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/Nucleotide Reverse Transcriptase Inhibitor).

**Storage.** Emtricitabine and tenofovir tablets should be kept in a tightly closed container.

**Additional information.** Strength in the current WHO Model list of essential medicines: 200 mg Emtricitabine and 300 mg Tenofovir disoproxil fumarate.

#### REQUIREMENTS

Comply with the monograph for 'Tablets'.

**Definition.** Emtricitabine and tenofovir tablets contain Emtricitabine and Tenofovir disoproxil fumarate. They contain not less than 90.0% and not more than 110.0% of the amounts of emtricitabine ( $C_8H_{10}FN_3O_3S$ ) and tenofovir disoproxil fumarate ( $C_{19}H_{30}N_5O_{10}P_2C_4H_4O_4$ ) 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 tablets. They ensure that, if tested, the tablets would comply with a water content limit of not more than 60 mg/g when determined as described under 2.8 Determination of water by the Karl Fischer method, Method A, using about 0.5 g of the powdered tablets.

#### Identity tests

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

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 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 l of each of the following solutions. For solution (A) disperse a quantity of powdered tablets in methanol R to obtain 5 mg of Emtricitabine per ml, filter and use the filtrate. For solution (B) use 5 mg of emtricitabine RS per ml in methanol R. For solution (C) use 7.5 mg of tenofovir disoproxil fumarate RS per ml in methanol R. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or in a current of air. Examine the chromatogram in ultraviolet light (254 nm).

One of the two principal spots obtained with solution A corresponds in position, appearance and intensity with that obtained with solution B and the other one corresponds with that obtained with solution C.

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 vapour and examine the chromatogram in daylight.

One of the two principal spots obtained with solution A corresponds in position, appearance and intensity with that obtained with solution B and the other one corresponds with that obtained with solution C.

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 50 volumes of heptane R, 30 volumes of glacial acetic acid R and 20 volumes of dichloromethane R as the mobile phase. Apply separately to the plate 5 l of each of the following solutions. For solution (A) disperse a quantity of powdered tablets in ethanol R to obtain 10 mg of Tenofovir disoproxil fumarate per ml, filter and use the filtrate. For solution (B) use 2 mg of fumaric acid R per ml of ethanol R. Develop the plate in an unsaturated tank over a path of 10 cm. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or in a current of air. Examine the chromatogram in ultraviolet light (254 nm).

One of the spots 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 above under test B.1 but using silica gel R5 as the coating substance. Spray lightly with a 16 g/l solution of potassium permanganate R and examine the chromatogram in daylight.

One of the spots obtained with solution A corresponds in position, appearance and intensity with that obtained with solution B.

C. See the test described under Assay. The retention times of the principal peaks in the chromatogram obtained with the test solution are similar to those due to emtricitabine, tenofovir disoproxil and to fumarate in the chromatogram obtained with the reference solution.

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## 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 0.01 M hydrochloric acid, and rotating the paddle at 50 revolutions per minute. At 45 minutes withdraw a sample of 10 ml of the medium and filter. Allow the filtered sample to cool to room temperature and dilute if necessary [solution (1)]. Prepare solution (2) containing 0.22 mg/ml of emtricitabine RS and 0.33 mg/ml of tenofovir disoproxil fumarate RS in the dissolution medium. Determine the content of emtricitabine ( $C_8H_{10}FN_3O_3S$ ) and tenofovir disoproxil fumarate ( $C_{19}H_{30}N_5O_{10}P,C_4H_4O_4$ ) as described under Assay using solution (1) and solution (2).

For each of the six tablets tested, calculate the total amount of emtricitabine ( $C_8H_{10}FN_3O_3S$ ) and tenofovir disoproxil fumarate ( $C_{19}H_{30}N_5O_{10}P,C_4H_4O_4$ ) in the medium from the results obtained. The amount in solution for each tablet is not less than 75% of the amount stated on the label. 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%.

## 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 octadecylsilyl groups (5  $\mu$ m). (Hypersil BDS column).

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: 5 volumes of phosphate solution and 95 volumes of water R.

Mobile phase B: 70 volumes of acetonitrile R, 5 volumes of phosphate solution and 25 volumes of water R.

Prepare the phosphate solution by dissolving 27.22 g of potassium dihydrogen phosphate R in 1000 ml of water R.

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0 – 9	93	7	Isocratic
9 – 15	93 to 0	7 to 100	Linear gradient
15 – 19	0	100	Isocratic
19 – 19.1	0 to 93	100 to 7	Return to initial composition
19.1–30	93	7	Re-equilibration

After preparation, keep the solutions at about 6 °C, or use an injector with cooling. Prepare the following solutions using a mixture of 20 volumes of acetonitrile R and 80

volumes of water R as a diluent. For solution (1) weigh and powder 20 tablets. Disperse a quantity of the powder containing about 10 mg of Tenofovir disoproxil fumarate, accurately weighed in 100 ml of the diluent and filter. For solution (2) dissolve quantities of tenofovir disoproxil fumarate RS and emtricitabine RS in the diluent to obtain a concentration of 0.1 mg/ml and 66.7 µg/ml of tenofovir disoproxil fumarate and emtricitabine, respectively. If necessary, adapt the concentration of solution (2) according to the ratio of Emtricitabine and Tenofovir disoproxil fumarate in the tablets. For solution (3) use 0.02 mg of fumaric acid R per ml of water R.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 280 nm.

Maintain the column temperature at 35 °C.

Inject alternatively 20 µl each of solutions (1), (2) and (3).

The test is not valid unless in the chromatograms obtained with solutions (1) and (2) three well-separated peaks are shown.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the content of emtricitabine (C<sub>8</sub>H<sub>10</sub>FN<sub>3</sub>O<sub>3</sub>S) and tenofovir disoproxil fumarate (C<sub>19</sub>H<sub>30</sub>N<sub>5</sub>O<sub>10</sub>P<sub>1</sub>C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>) in the tablets.

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## Sulfadoxine and pyrimethamine tablets

Revised draft proposal for *The International Pharmacopoeia* (March 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: 500 mg sulfadoxine and 25 mg pyrimethamine.

### REQUIREMENTS

Comply with the monograph for 'Tablets'.

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**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 ethylacetate R, 25 volumes of methanol R and 1 volume of glacial acetic acid R as the mobile phase. Apply separately to the plate 10  $\mu$ l 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 5 mg 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 for 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%.

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## 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 RS 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 and pyrimethamine 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 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%).

## 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.)

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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- $\mu$ m 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  $\mu$ l 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.

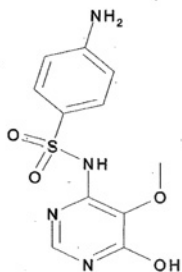
Inject alternately 20  $\mu$ l each of solutions (1) and (4).

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,  $C_{12}H_{13}N_4O$ , in the tablets.

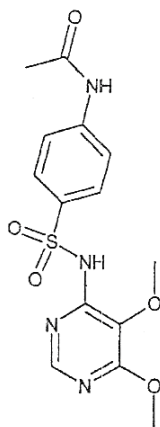
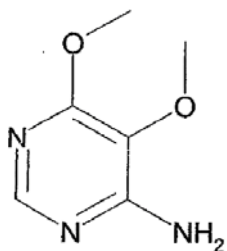
### Impurities

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. M-(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 the Secretariat: structures and chemical names for related substances to be confirmed]*

# Recent Publications, Information and Events

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## Life-saving antivenoms: guidelines and database

**World Health Organization** — Snake bites kill at least 100 000 people a year and for countries facing a shortage of appropriate antivenoms, access to and information about available antivenoms is increasingly important. WHO has published new guidelines for the production, regulation and control of snake antivenoms and provides a dedicated web site with details on where the venomous snakes are located, what they look like, which antivenoms are appropriate, and where they can be obtained.

The guidelines provide details for the production, regulation and control of snake antivenoms while the online database identifies venomous snake species (including information and colour photographs) for which availability of appropriate antivenoms should be prioritized.

**Reference:** World Health Organization. <http://www.who.int/bloodproducts/snakeantivenoms>

## Sources of paediatric medicines

**World Health Organization** — To address problems associated with production and provision of paediatric medicines, especially in the developing world, the United Nations Children's Fund (UNICEF) and WHO have released a new publication that lists medicines formulated for children to help doctors and organizations obtain some of the 240 essential medicines that can save the lives of children.

The second edition of *Sources and Prices of Selected Medicines for Children* offers

current details on 612 different paediatric formulations of 240 medicines selected from the WHO Model List of Essential Medicines for Children, as well as therapeutic food, vitamin and mineral supplements to treat major childhood illnesses and diseases.

WHO recommends that medicines for children should be provided as flexible, solid, oral dosage forms that can be administered in a liquid when given to a sick child. Liquid formulations are more expensive to buy compared with dispersible tablets and are also more costly to store, package, and transport safely.

**Reference:** World Health Organization. <http://www.who.int/medicines>

## Multidrug and drug- resistant tuberculosis

**World Health Organization** — A new, global WHO report on extensively drug-resistant (M/XDR-TB) tuberculosis examines the trends, progress and challenges in treating these forms of tuberculosis. In some parts of the world, one in four people with tuberculosis becomes ill with a form of the disease that can no longer be treated with standard drugs. Drug-resistant tuberculosis is now at record levels.

In *Multidrug and Extensively Drug-Resistant Tuberculosis: 2010 Global Report on Surveillance and Response*, it is estimated that 440 000 people had MDR-TB worldwide in 2008 and that a third of them died. Tuberculosis programmes face tremendous challenges in reducing MDR-TB rates. The report presents drug resistance data from 114 countries and updated information from

35 of them. Despite the growing understanding of the magnitude and trends in drug-resistant TB, major gaps remain in geographical areas covered. Since 1994, only 59% of all countries globally have been able to collect high quality representative data on drug resistance. There is an urgent need to obtain information, particularly from Africa and those high MDR-TB burden countries where data have never been reported: Bangladesh, Belarus, Kyrgyzstan, Nigeria and Pakistan. Moreover, countries need to expand the scope of their surveys to cover entire populations, repeat surveys are needed to better understand trends in drug resistance and countries need to move towards adopting systematic continuous surveillance.

**Reference:** *Multidrug and Extensively Drug-Resistant Tuberculosis: 2010 Global Report on Surveillance and Response*. March 2010 at <http://www.who.int/publications/en>

## Guidelines for the treatment of malaria

**World Health Organization** — *Guidelines for the treatment of malaria* provides evidence-based and up-to-date recommendations for countries on malaria diagnosis and treatment.

The guidelines cover the diagnosis and treatment of uncomplicated and severe malaria caused by all types of malaria, including in special groups (young children, pregnant women, HIV /AIDS), in travellers (from non-malaria endemic

regions) and in epidemics and complex emergency situations.

This second edition introduces a fifth artemisinin combination therapy (ACT) to the four already recommended. Furthermore, the guidelines recommend parasitological confirmation of diagnosis in all patients suspected of having malaria before treatment. The move towards universal diagnostic testing of malaria is a critical step forward in the fight against malaria as it will allow for the targeted use of ACTs for those who actually have malaria.

**Reference:** *Guidelines for the Treatment of Malaria*. Second Edition. at <http://www.who.int/publications/en>

## Where there are no pharmacists

A new Book, *Where There Are No Pharmacists*, has recently been launched by Health Action International Asia-Pacific (HAIAP).

*Where There Are No Pharmacists* is about managing medicines. It explains in easy English how to order, store, prepare, dispense and use medicines safely and effectively. This book provides advice on all these aspects for people working with medicines as well as information to help communities benefit from the use of medicines.

**Reference:** Health Action International Asia-Pacific at <http://www.twinside.org.sg/>