WHO Drug Information

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Access to Blood Products

Access to safe and effective blood products in low and middle income countries

Blood products include blood and blood components produced as single-donor products for direct transfusion, so-called labile blood components (i.e., red blood cells, platelets and plasma), as well as numerous plasma-derived medicinal products (e.g., albumin, polyclonal and specific immunoglobulins, and blood coagulation factors) that are prepared in fractionation facilities from pools of thousands of plasma units.

In high-income countries (HIC), each unit of whole blood collected is separated into several therapeutic blood components to both deliver the most effective treatment (component therapy) and to make most efficient use of a precious and limited human resource. The plasma component can be used directly for transfusion, or sent for further manufacture into therapeutic plasma protein concentrates.

Access to safe and effective blood products is a major challenge in low and middle income countries (LMIC) where local blood establishments may have very basic facilities and systems, where quality and safety standards need to be established or strengthened, and where blood supplies may be insufficient to meet medical needs.

World Health Assembly resolution WHA63.12, in addressing the availability, quality and safety of blood products, points out that in many LMIC a large percentage of human plasma, separated from whole blood is currently discarded. This wastage occurs in large part because the separated plasma is not suitable for further manufacture. Generally accepted international standards require, among other things, appropriate freezing and cold storage conditions, traceability of donors, testing to lower the residual viral risk, regulatory controls, quality systems and adherence to good manufacturing practices (GMP). Improvement in quality standards, know-how and production processes in blood establishments should therefore directly contribute to reducing the rate of transmission by transfusion of blood-borne infectious diseases.

Even while the need for plasma products grows, a substantial and increasing volume of recovered plasma in LMIC is currently being wasted. This volume has been estimated — based on the global approximations of whole blood donations and the volume of recovered plasma currently used for direct transfusion or for fractionation — to be close to 9.3 million litres each year. This volume corresponds to more than 40% of world supply of recovered plasma.

The volume of discarded plasma is expected to increase substantially as the volume of blood collected to meet projected LMIC needs for red cells (the primary determinant of the number of whole blood collections) increases and as blood component therapy becomes more widely applied. This has been the experience supported by decades of clinical data from HIC.

The challenge now is to support LMIC investment in improving the quality of the blood they collect by improving the knowledge base, infrastructure, production standards and regulatory oversight in blood establishments and by emphasizing the positive impact that such a move
will have on public health. The short-term investment in improving local production standards in blood establishments of countries currently discarding large volumes of plasma is a means to improve access to essential plasma-derived medicinal products while at the same time improving the quality and safety of the other blood components, the safety and health of the blood donor and the long-term benefits to the public health of national and worldwide populations.

To examine and analyze the available data, the drivers of technology transfer and local production in blood establishments, and the potential benefits and risks that arise from such an initiative, WHO convened a stakeholders’ workshop in Geneva on 14–15 June 2012. Participants included representatives from national regulatory authorities, blood collection organizations, patient organizations, national blood programmes, plasma fractionators, members of the WHO Blood Regulators Network, nongovernmental organizations, public health and funding agencies.

The report of these deliberations will be published in April 2013 and posted at the web site address: http://www.who.int/bloodproducts. The report examines the volume of plasma separated from whole blood that is currently wasted worldwide and identifies challenges and opportunities and the key steps needed to improve the current situation.

The steps proposed should have multiple benefits, at the national, regional and global levels. They include strengthening local production capacity in blood establishments in countries currently discarding plasma, through transfer of technology and know-how, building technical capacity and expertise of national regulatory authorities in the whole-blood area, improving the health of the blood donor and blood-product recipient, and providing data on the epidemiology and demographics of markers of blood-borne infections.

Overall, it is imperative for governments in LMIC to address the large wastage of blood and plasma estimated to occur, and it is clearly in their interest to do so. The process, methods, and timelines for improving blood collection systems will vary in different countries. The gaps between HIC and LMIC are significant, but differ from region to region. Suitable regulatory oversight is often lacking, and in its absence progress will be faltering and at risk. Sustainability of aid provided to many countries, largely because of the AIDS pandemic, will only occur with the exertion of national will and locally appropriate regulatory and legislative action.

Another initiative intended to improve the safety, availability, quality, and accessibility of blood products is the proposal endorsed by the WHO Blood Regulators Network to add whole blood and red blood cells to the WHO Model List of Essential Medicines (EML). This proposal was also endorsed by the 63rd WHO Expert Committee on Biological Standardization and the 15th International Conference of Drug Regulatory Authorities. Whole blood and red cells meet the generally accepted definition of medicines; they are among the most widely prescribed therapies (an estimated 90 million units annually worldwide), and are credited with saving millions of lives each year.

Blood is a national resource, derived from voluntary public donations and processed into medicines to advance that same public’s health. Blood is a unique biological in that the “raw material” is the blood donor and the health of that donor is linked directly to the health of the recipient. The EML designates medicines as essential based on their efficacy and safety, availability, ease of use in different settings, comparative cost-effectiveness, and public health
need as judged by disease prevalence. The EML is important because in many countries it forms the basis of national drug policies. Governments and health ministries often refer to the EML when making decisions regarding resource allocation and health spending.

Adding blood to the EML should encourage investment in building local systems to provide safe and effective blood which is accessible to more patients. Although the cost of upgrading standards, infrastructure and regulatory oversight requires an initial investment, the result is safer available blood, reduction in the risk of another epidemic of blood-borne disease transmission, and long-term societal benefit. Most HIC already distinguish blood components as a product in terms of preparation, storage and handling, from the process of transfusion which has traditionally been considered medical practice, and many already regulate blood components as medicines.

There is no conflict between the concepts of blood as a medicine and blood donation as an altruistic act. The opposite is true. Addition of whole blood and red blood cells to the EML should benefit the development of voluntary non-renumerated donation by protecting the health of the blood donor and by raising the standards for safe collection, accurate screening and testing, and follow-up of donors who require care. Countries that already regulate blood as a medicine oversee and protect the appropriate care of the donor. Nor is there evidence that regarding blood as a medicine will promote commercialism of human tissue by introducing the sale of blood or payment of donors. In virtually all countries that have regulated blood as a medicine for decades, blood components derive from voluntary, unremunerated donors. Listing blood on a WHO-sponsored document should further emphasize the importance of voluntary non-renumerated blood donation and the not-for-profit status of blood collecting organizations: policies that WHO has endorsed for many years. In all cases, the purpose of the EML is to reduce the burden of disease. The application to add blood to the EML will encourage governments to invest in infrastructure and the governance of blood systems, support safe blood collection and regulated blood preparation, storage and shipment, and improve public health.

At the 15th International Conference of Drug Regulatory Authorities, regulators from more than 100 countries endorsed the recommendations that:

- Member States should take steps to assure the quality, safety and availability of blood for transfusion, including oversight through regulation; and

- Member States are encouraged to establish lists of essential medicines and to include whole blood and blood components for transfusion on their lists.

These recommendations underline the objectives of Resolution WHA63.12 adopted in 2010 which supports access to quality, safe blood products at the global level.
Mechanism to combat substandard/spurious/falsely-labelled/falsified/counterfeit medical products

The Member State Mechanism on Substandard/spurious/falsely-labelled/falsified/counterfeit (SSFFC) Medical Products was established in May 2011 by the World Health Assembly at its sixty-fifth session. The goal of the SSFFC Mechanism is to promote international collaboration on strategies to address the falsification of medicines from the standpoint of public health, excluding trade and intellectual property considerations.

The first meeting of the Member State Mechanism on SSFFC Medical Products, was organized by the World Health Organization (WHO) and the Argentine Ministry of Health. On 21 November 2012, representatives from sixty-five WHO Member States met in Buenos Aires, Argentina, and agreed to promote strengthening of action to combat SSFFC medical products. The meeting ended with a call to all countries to jointly address this global public health problem that affects millions of people worldwide.

The 200 representatives at the meeting agreed on a workplan that highlights the importance of cooperation between different national authorities and the sharing of best practices and experiences. They agreed to establish a global committee comprising two delegates from each WHO Region to support implementation of a workplan which provides for the reinforcement of national regulatory bodies through capacity-building and networking.

The meeting also stressed the need to develop educational initiatives targeted at consumers, health professionals and industry to prevent SSFFC medical products. It called for the development of methodologies and instruments to obtain more accurate information on the nature and magnitude of the problem. Participants advocated the establishment of guidelines on how to respond to the detection of SSFFC medicines and on securing the distribution chain to avoid the infiltration of SSFFC medical products.

The manufacture, distribution and sale of SSFFC medical products is a problem that endangers the health of the population within all regions and Member States, and impacts on the credibility of health services. Globalization, free trade and Internet technology have all affected the way in which patients obtain their medicines and have made it more complex for national regulatory authorities to effectively control the distribution systems in their countries.

Through the Mechanism, WHO will also enable strengthening of national and regional capacity by developing strategies to prevent SSFFC medical products reaching patients.

Reference: SSFFC Mechanism and activities related to SSFFC medical products at http://www.who.int/medicines

Speeding up access to quality medicines in Africa

Ten African countries have joined a WHO initiative that aims to speed up access to medicines and develop local expertise in medicines regulation.
The Accelerated Registration Pilot Project is a new collaborative activity between medicines regulators in developing countries and international experts working with WHO’s Prequalification of Medicines Programme. WHO’s list of prequalified products is a vital tool for United Nations agencies and other organizations involved in bulk purchasing of medicines. The list includes medicines that have been evaluated for quality, safety and efficacy based on information from manufacturers and inspection of manufacturing and clinical sites.

The Accelerated Registration Pilot Project encourages national regulatory authorities to fast track the registration of medicines that have already been assessed and approved by WHO’s prequalification procedure. In many countries, the same medicines are also required to go through a national process of quality assurance before their use is authorized. This is a lengthy, expensive procedure that can discourage or delay pharmaceutical companies from applying to import their products.

The Global Fund to Fight AIDS, Tuberculosis and Malaria encourages use of the accelerated registration initiative and urges national authorities to use prequalification conclusions to avoid duplicating work and spending time and money on a procedure that has already been carried out. Some national medicines regulatory authorities may have limited resources and this project will help them to benefit from the international expertise and rigorous standards of WHO’s Prequalification of Medicines Programme.

Within the project, when a manufacturer applies to register a prequalified product in a participating country, it agrees to share the complete prequalification assessment and inspection file with a nominated person from the national regulatory authority via a secure internet site. The national authority may use the prequalification reports to make an independent decision on whether to register the medicine in that country. This provides an opportunity to take advantage of WHO prequalification without losing national autonomy.

The initiative establishes strong lines of communication on assessment and inspection outcomes with medicines regulatory authorities in developing countries and could serve as a model for collaboration among the authorities themselves, particularly in countries with similar health needs.

In countries which lack experts in medicines regulation, particularly in the assessment of quality and efficacy of medicines, the pilot project is an opportunity to build capacity and learn from best practices. It also provides a forum for information sharing and exchange with WHO’s prequalification experts who are drawn from well-resourced regulatory authorities around the world.

A major focus is on getting products registered and maintaining a two-way flow of information once the product is in use. WHO will inform the national authority of any withdrawals, suspensions or delisting of prequalified medicines and they, in turn, will keep WHO informed of any national deregistration or issues about the medicine’s safety or efficacy.

The accelerated registration project has the potential to improve medicines registration globally. Besides making treatment available to patients more rapidly, it also has a positive effect on training and capacity building in the partner countries, and gives them the ultimate responsibility for their own systems.

PQM technical support for prequalification of medicines

The Programme for Promoting the Quality of Medicines (PQM) is funded by the US Agency for International Development (USAID) and implemented by the US Pharmacopeial Convention (USP). Its aim is to increase the availability of affordable, high-quality medicines to treat patients worldwide suffering from multidrug-resistant tuberculosis by providing technical assistance at no cost to manufacturers. The initiative has yielded its first antituberculosis medicine, cycloserine, 250 mg capsule, which has now achieved prequalification status from the World Health Organization (WHO).

The WHO Prequalification of Medicines Programme (PQP) evaluates and assures the quality of medicines bought by international aid programmes. This improves treatment results in developing countries and beyond. Given the policy of many organizations and agencies that only medicines prequalified by WHO or approved by a stringent regulatory authority are suitable for procurement, the increase in demand for prequalified products has stretched WHO’s resources.

To address this resource gap, the PQM programme — which also works to combat substandard and counterfeit medicines in developing countries and increase the supply of quality-assured medicines — offers technical assistance by providing support to interested manufacturers to achieve prequalification.

PQM may provide assistance during preparation of product dossiers for submission to PQP by guiding manufacturers toward compliance with WHO good manufacturing practices or by addressing WHO comments on manufacturer submissions. Assistance is particularly focused on «second-line» antituberculosis medicines used for multidrug-resistant tuberculosis. This form of tuberculosis is more difficult and lengthy to manage — often requiring up to two years of treatment. Poor-quality medicines can lead to drug resistance and undermine desired treatment outcomes.

By expediting the process of prequalification with WHO, PQM is able to expand the pool of viable manufacturers and, in turn, increase the supply of quality-assured medicines. Ultimately, these medicines can help prevent unnecessary patient deaths, particularly among vulnerable populations including many women and children.

In its efforts to improve access to quality-assured medicines, the PQM technical assistance programme also supports the Global Drug Facility (GDF) — a pooled procurement system for antituberculosis medicines operated by WHO. PQM, in collaboration with GDF, USAID and WHO, identify promising manufacturers who may then receive PQM technical assistance.

PQM offers technical assistance for twelve types of medications to treat multidrug-resistant tuberculosis. PQM is currently working with approximately twenty manufacturers of finished products or active pharmaceutical ingredients from around the world to prepare products for prequalification. Some of these manufacturers produce multiple second-line tuberculosis medicines.

Through a series of workshops held in conjunction with WHO and GDF, PQM has been reaching out to manufacturers in regions of the world with a high burden of tuberculosis or where manufacturers are working to improve their manufacturing practices.

International Generic Drug Regulator’s Pilot Project

The International Generic Drug Regulator’s Pilot Project (IGDRP) was created to promote regulatory collaboration and convergence in generic drug regulatory programmes in order to address challenges posed by increasingly heavy workloads, globalization, and the growing complexity of scientific issues.

Following on from its previous meeting in Washington, D.C. in April 2012, IGDRP representatives from the medicines regulatory authorities of Australia, Brazil, Canada, China, Chinese Taipei, Japan, Republic of Korea, Mexico, Singapore, Switzerland and the United States of America, as well as the World Health Organization and the European Directorate for the Quality of Medicines and Healthcare, met in Nanchang, China from 3–4 December 2012.

Representatives discussed worksharing possibilities in the areas of active substance master files (ASMFs)/drug master files (DMFs), exchange of confidential information, inspection of sites conducting bioequivalence and bioanalytical studies, conditions associated with granting biowavers, and pharmaceutical quality issues.

Potential efforts to assist WHO in implementing proposed changes to the WHO Prequalification of Medicines Programme as it moves toward a new operating model were also canvassed, as were the operational possibilities of a number of secure platforms for the sharing of confidential information between agencies. The next meeting of the IGDRP is tentatively scheduled for April or May 2013 in Australia.

Reference: Prequalification of Medicines Programme at http://www.who.int/prequal
Safety and Efficacy Issues

Tolvaptan: risk of liver injury

United States of America — Healthcare professionals have been notified of significant liver injury associated with the use of tolvaptan (Samsca®).

In a double-blind, placebo-controlled trial in about 1400 patients with autosomal dominant polycystic kidney disease (ADPKD) and its open-label extension trial, three patients developed significant increases in serum alanine aminotransferase with concomitant, clinically significant increases in serum total bilirubin. In the trials, the maximum daily dose administered (90 mg in the morning and 30 mg in the afternoon) was higher than the maximum 60 mg daily dose approved for the treatment of hyponatraemia.

Tolvaptan is a selective vasopressin V2-receptor antagonist indicated for the treatment of clinically significant hypervolaemic and euvolaemic hyponatraemia. Samsca® is not approved for the treatment of ADPKD.

Most of the liver enzyme abnormalities were observed during the first 18 months of therapy. Following discontinuation of treatment, all three patients improved. An external panel of experts assessed these cases as being either probably or highly likely to be caused by tolvaptan. These findings indicate that tolvaptan has the potential to cause irreversible and potentially fatal liver injury. These data are not adequate to exclude the possibility that patients receiving tolvaptan for its indicated use of clinically significant hypervolaemic and euvolaemic hyponatraemia are at a potential increased risk for irreversible and potentially fatal liver injury.

Healthcare providers should perform liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. If hepatic injury is suspected, tolvaptan should be promptly discontinued, appropriate treatment should be instituted, and investigations should be performed to determine probable cause. Tolvaptan should not be re-initiated in patients unless the cause for the observed liver injury is definitively established to be unrelated to treatment with tolvaptan.


Roflumilast: risk of suicidal behaviour

United Kingdom — Roflumilast (Daxas®) is a phosphodiesterase-type-4 (PDE4) inhibitor used for maintenance treatment of severe chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis. It is indicated for adult patients with a history of frequent exacerbations as an add-on to bronchodilator treatment. The recommended dose is one 500 microgram tablet daily.

From clinical trial data, roflumilast is known to be associated with an increased risk of psychiatric disorders such as insomnia, anxiety, nervousness and depression. Rare instances of suicidal ideation and behaviour, including completed suicide, have also been observed. A recent review of post-marketing data (unpublished) has found that cases of suicidal behaviour have also
been reported in patients with and without a history of depression, usually in the first weeks of treatment.

If patients have existing psychiatric symptoms, or if concomitant treatment is intended with other medicines likely to cause psychiatric symptoms, roflumilast treatment should only be started or continued after careful assessment of the benefits and risks.


Sodium picosulfate/magnesium citrate: convulsions

Canada — Pico-Salax® contains sodium picosulfate and magnesium citrate (also referred to as citric acid and magnesium oxide) and is available as a nonprescription oral purgative indicated for the clearance of the bowel prior to x-ray examination, endoscopy or surgery (1). In addition to Pico-Salax®, there are four other marketed medications containing sodium picosulfate/magnesium citrate in Canada: Picodan®, Purg-Odan®, Picoflo® and Oral Purgative®.

Pico-Salax® acts as an osmotic laxative, stimulates peristalsis and has a powerful washing out effect within 3 to 6 hours or less of administration (1). The diarrhoea produced by the medication can lead to dehydration and loss of electrolytes, particularly sodium which may result in hyponatraemia and convulsions (1–3). Elderly and debilitated individuals are particularly at risk. Pico-Salax® may also decrease the absorption of oral medications due to an increase in gastrointestinal transit rate, and may be associated with convulsions in patients taking anticonvulsants (1).

As of 30 June 2012, Health Canada has received 11 reports of convulsions suspected of being associated with Pico-Salax®. Several articles in the literature reported incidents of seizures and hyponatraemia or emphasized the risk of electrolyte disturbances when using sodium picosulfate/magnesium citrate (4–7). It is important to replace electrolytes as well as fluids when rehydrating (8). Both the risk of hyponatraemia and decreased drug absorption are well described in the prescribing and consumer information for Pico-Salax® (1).

Extracted from the Canadian Adverse Reaction Newsletter, Volume 23, Number 1, January 2013 at http://www.hc-sc.gc.ca/dhp-ms/medeff/bulletin/carn-bcei_v23n1-eng

References


As of 30 June 2012, Health Canada has received five reports of rhabdomyolysis independent of NMS suspected of being associated with risperidone. All but one patient had recovered at the time of reporting. No deaths were reported. Reports of significant and transient elevation of CPK in stable patients without the presence of NMS involving risperidone and other antipsychotics have been described in the literature (3, 10, 11). However, the exact pathophysiological mechanism that mediates this association remains unclear. There are individual vulnerability factors involved in the development of rhabdomyolysis in the presence of antipsychotics (12). It has also been proposed, based on animal studies, that the accumulation of serotonin in skeletal muscle can play a role in the development of muscle injury (11). Health professionals should be aware of the risk of rhabdomyolysis without the presence of NMS suspected of being associated with the use of risperidone.

Extracted from the Canadian Adverse Reac-
tion Newsletter, Volume 23, Number 1, January 2013 at http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v23n1-eng

References


**Docetaxel: serious respiratory-related adverse reactions**

**Canada** — Docetaxel (Taxotere®) is an injectable chemotherapy drug that was first marketed on 31 December 1995. It is currently indicated for the treatment of cancer: breast, non-small cell lung, ovarian and prostate, as well as squamous cell carcinoma of the head and neck (1). Currently, there is one generic product marketed in Canada.

Docetaxel belongs to a group of antineoplastic medicines known as taxanes which act by disrupting the microtubular network essential for cell division (1). Specifically, it promotes the assembly and stabilization of microtubules and leads to the production of microtubule bundles without normal function, resulting in the inhibition of mitosis in cells.

Several antineoplastic drugs, including docetaxel, have been known to induce pulmonary toxicity, which may result in a variety of pathological syndromes ranging from unspecified dyspnea to pulmonary pneumonitis that may lead to permanent pulmonary fibrosis and possible death (2–3). This type of drug-associated lung injury typically occurs as a result of cellular dysfunction which can trigger apoptosis or by impairing the cell and tissue repair sequence (4).

As of 31 July 2012, Health Canada has received 31 reports of respiratory-related adverse reactions suspected of being associated with docetaxel involving pneumonitis, interstitial lung disease (ILD), lung infiltration or respiratory failure. Among these cases, 23 patients required hospitalization. A fatal outcome was reported in nine cases.

Several cases of serious respiratory-related adverse reactions in patients using docetaxel, either alone or in combination with other antineoplastic agents, have been reported in the literature. Reported adverse reactions include pneumonitis or interstitial pneumonitis, pulmonary infiltrates, acute respiratory distress syndrome, respiratory failure, ILD, interstitial infiltrates and pneumocystis pneumonia. Some of these cases resulted in fatal outcomes (5).

Extracted from the Canadian Adverse Reaction Newsletter, Volume 23, Number 1, January 2013 at http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v23n1-eng

**References**


Zolpidem: impaired activity

United States of America — The Food and Drug Administration (FDA) has notified the public of new information about zolpidem, prescribed for insomnia. New data show that blood levels in some patients may be high enough the morning after use to impair activities that require alertness, including driving. Zolpidem-containing products and generics include Ambien®, Ambien CR®, Edluar®, and Zolpimist®.

Healthcare professionals are urged to caution all patients using zolpidem products about the risks. Data show the risk for next-morning impairment is highest for patients taking the extended-release forms of these drugs (Ambien CR® and generics). Women appear to be more susceptible to this risk because they eliminate zolpidem from their bodies more slowly than men.

The recommended dose of zolpidem for women should now be lowered from 10 mg to 5 mg for immediate-release products and from 12.5 mg to 6.25 mg for extended-release products (Ambien CR®). The FDA has also informed the manufacturers that, for men, the labeling should recommend that healthcare professionals consider prescribing the lower doses — 5 mg for immediate-release products and 6.25 mg for extended-release products.

The recommended dose for Intermezzo®, a lower dose zolpidem product approved for middle-of-the-night awakening, is not changing. At the time of approval in November 2011, the label already recommended a lower dosage for women than for men. The FDA has prepared a list of questions and answers as an overview of this safety issue.


Combination treatment with telaprevir, peginterferon alfa and ribavirin: serious skin reactions

United States of America — The Food and Drug Administration (FDA) has received reports of serious skin reactions, some fatal, in patients taking the hepatitis C drug telaprevir (Incivek®) in combination with the drugs peginterferon alfa and ribavirin (Incivek® combination treatment). Significantly, some patients died when they continued to receive Incivek® combination treatment after developing a worsening, or progressive rash and systemic symptoms. As a result, FDA has added a boxed warning to the drug label stating that Incivek® combination treatment must be immediately stopped in patients experiencing a rash with systemic symptoms or a progressive severe rash. Consideration should also be given to stopping any other medications that may be associated with serious skin reactions. Typical systemic symptoms and signs may include fever, nausea, diarrhoea, mouth sores or ulcers, facial edema, red or inflamed eyes, swelling or hepatitis. All patients with serious skin reactions should also receive urgent medical care.

Incivek® is a hepatic C virus NS3/4A protease inhibitor indicated in combination with peginterferon alfa and ribavirin for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease, including patients who have cirrhosis, are treatment-naïve, or who have been previously received interferon-based treatment. Incivek® must always be used in combination with peginterferon alfa and ribavirin.
Serious skin reactions, including drug rash with eosinophilia and systemic symptoms (or DRESS) and Stevens-Johnson Syndrome (SJS) have been previously reported in patients taking Incivek® combination treatment. If serious skin reactions occur, all three components of Incivek® combination treatment must be immediately discontinued.


Dabigatran etexilate mesylate: not for patients with mechanical prosthetic heart valves

United States of America — Healthcare professionals have been notified that the anticoagulant dabigatran etexilate mesylate (Pradaxa®) should not be used to prevent major thromboembolic events in patients with mechanical heart valves, also known as mechanical prosthetic heart valves. The RE-ALIGN clinical trial conducted in Europe (1) was recently stopped because Pradaxa® users were more likely to experience strokes, heart attacks, and blood clots forming on the mechanical heart valves than were users of the anticoagulant warfarin. There was also more bleeding after valve surgery in Pradaxa® users than in the warfarin users.

Dabigatran is approved to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation. It is not approved for patients with atrial fibrillation caused by heart valve problems. The FDA is requiring a contraindication of dabigatran for patients with mechanical heart valves. Healthcare professionals should promptly transition any patient with a mechanical heart valve who is taking dabigatran to another medication.

The use of dabigatran in patients with another type of valve replacement made of natural biological tissue, known as a bioprosthetic valves, has not been evaluated and cannot be recommended.

References


Sodium oxybate with alcohol or drugs: respiratory depression

United States of America — The Food and Drug Administration (FDA) is reminding healthcare professionals and patients that the combined use of sodium oxybate (Xyrem®) with alcohol or central nervous system (CNS) depressant drugs can markedly impair consciousness and may lead to respiratory depression.

The use of alcohol with Xyrem® is a new contraindication added to the label, which already contraindicates its use with insomnia drugs. Use with other CNS depressant drugs such as opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, general anesthetics, and muscle relaxants should be avoided.

Sodium oxybate is approved to reduce cataplexy and treat daytime sleepiness in patients with narcolepsy. Sodium oxybate is also known as gamma-hydroxybutyrate (GHB). GHB is a known drug of abuse associated with central nervous system (CNS) adverse events, including death. Even at recommended doses, Xyrem® can cause confusion, depression, and other neuropsychiatric events.

Statins: risk of increased blood sugar levels and diabetes

Canada — Health Canada has announced a labelling update for all statins regarding the risk of increased blood sugar levels and a small increased risk of diabetes among patients already at risk for the disease.

Based on the review of all available data, Health Canada concluded that the risk of diabetes appears to be mainly in patients with pre-existing risk factors for diabetes, such as high levels of glucose or triglycerides, obesity or high blood pressure. Health Canada continues to believe the overall cardiovascular benefits of statin drugs in reducing blood cholesterol outweigh their risks.

A new warning about increased blood sugar levels and the risk of diabetes, including information on how to identify high-risk patients, has been added to the drug labels for the six statins currently marketed in Canada: atorvastatin, lovastatin, rosuvastatin, simvastatin, pravastatin and fluvastatin.


Immunomodulatory medicines: progressive multifocal leukoencephalopathy

Australia — Immunomodulatory medicines have been associated with the development of progressive multifocal leukoencephalopathy. Awareness of risk factors and early recognition of symptoms is important as early diagnosis is likely to improve the prognosis (1).

Progressive multifocal leukoencephalopathy (PML) is a rare, but often fatal, demyelinating disease of the central nervous system. PML lesions are typically asymmetrical demyelinated plaque areas with irregular borders, surrounded by macrophages and irregular astrocytes with large, multiple nuclei (2). Patients with PML can have a variety of symptoms including muscle weakness, sensory deficit, cognitive dysfunction, language impairment and/or coordination and gait difficulties (3).

PML is caused by a human polyomavirus, the JC virus. Approximately 50% of the world’s population are infected with the virus by the time they reach age 20, although most remain asymptomatic (4). After initial virus infection, the virus remains quiescent in the kidneys, bone marrow and lymphoid tissue (3).

In immunocompromised individuals the quiescent virus can reactivate, enter the bloodstream and then gain entry to the central nervous system where it infects oligodendrocytes and astrocytes. Infection of these cells leads to cell death, and the resulting demyelination produces the neurological signs and symptoms of PML (5). Viruses isolated from the brains of individuals with PML have a genomic rearrangement in the regulatory region that is not found in the strains responsible for initial infection (4,5).

Cell-mediated immunity disorders are the major immunological disorders that predispose individuals to the development of PML (4). Cases have been reported in patients with HIV, lymphoproliferative disorders, malignancies, patients on immunosuppressive therapy after solid organ transplantation and in rheumatic diseases such as systemic lupus erythematosus (6,7).

Immunosuppressive medications that have been associated with PML include cyclophosphamide, corticosteroids, mycophenolate mofetil and monoclonal antibodies including natalizumab, rituximab and alemtuzumab (8).

The early signs of PML are often related to cognitive dysfunction, manifesting
as mental slowness, disorientation and behavioural changes (2). Motor and sensory disturbance, characterized by lack of coordination, gait disturbance, ataxia, hemiparesis or visual deficits may also be found at the time of presentation (2). Seizures, language difficulties and headaches can occur but are less common. These signs and symptoms progress over the course of a few weeks and death can occur weeks to months after diagnosis.

**Australian and New Zealand reports of PML associated with immunomodulatory medicines (to 30 November 2012)**

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab*</td>
<td>13</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>13</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>1</td>
</tr>
<tr>
<td>Cyclophosphamide*</td>
<td>1</td>
</tr>
<tr>
<td>Prednisolone*</td>
<td>1</td>
</tr>
<tr>
<td>Mycophenolate mofetil#</td>
<td>1</td>
</tr>
<tr>
<td>Tacrolimus#</td>
<td>1</td>
</tr>
<tr>
<td>Dexamethasone#</td>
<td>1</td>
</tr>
</tbody>
</table>

* Co-suspect medicines in same report.
# Co-suspect medicines in same report.

Improved chance of survival is associated with early diagnosis, younger age at diagnosis and if the disease is limited to one lobe of the brain (1). Current treatment of PML is limited and is generally supportive in nature. A treatment strategy for PML in HIV-negative patients is to restore the host adaptive immune response by stopping or decreasing immunosuppression (3).

Recovery of the immune system can trigger immune reconstitution inflammatory syndrome (IRIS). In HIV-negative patients with PML-IRIS, the current treatment is corticosteroids to reduce the inflammatory response (3).

**References**


**Thyroxine and fractures**

**Australia** — Health professionals are advised that the product information for thyroxine (Eutroxsig® and Oroxine®) has recently been updated to include a precaution about the increased risk of osteoporotic fracture associated with excessive thyroxine doses. Control of hypothyroidism should be monitored regularly, especially in the elderly, and the thyroxine dose adjusted accordingly.

Chronic hyperthyroidism promotes bone turnover, characterized by increases in bone resorption and in urinary excretion of calcium and phosphorus. Increased
bone resorption may result in osteoporosis and an increased risk of fracture. A similar risk appears to exist for hypothyroid patients receiving higher-than-needed doses of thyroxine. The elderly may be at particularly increased risk, since thyroxine replacement needs decrease with age, and age is an additional risk factor for osteoporosis (1).

Fracture risk with thyroxine replacement therapy
Two recent large studies have examined the risk of fracture in patients on long-term thyroxine replacement. A nested case-control study in 213,511 Canadian thyroxine users aged over 70 followed patients for a mean of 3.8 years (1) and an observational cohort study in 17,684 Scottish thyroxine users aged 18 and over, was conducted with a median follow-up of 4.5 years (2). Although neither study measured both thyroxine and TSH levels, each found an association between either high or excessive (as measured by TSH suppression) thyroxine dose and fracture. As well as increasing the risk of osteoporosis, excess thyroxine may also increase the risk of falls secondary to arrhythmia or muscle weakness, particularly in the elderly (1).

The Product Information for thyroxine (Oroxine®, Eutroxsig®) has recently been updated with a new precaution about the effects of thyroxine on bone mineral density. It is recommended that patients receiving thyroxine are given the minimum dose necessary to achieve the desired clinical and biochemical response. Prescribers should keep in mind that replacement thyroxine needs decrease in the elderly and serum TSH should be monitored regularly and thyroxine doses adjusted accordingly. The risk of fracture may be greater in patients with other risk factors for osteoporosis, including postmenopausal women, those with a family history or past history of fracture or osteoporosis, smokers, and patients with vitamin D deficiency.


References

Oral bowel cleansing products: serious electrolyte disturbances
Australia — The use of oral bowel cleansing products is part of the preparation for a number of medical, diagnostic and surgical procedures. These products create a cathartic effect by osmotic action, resulting in a transfer of fluid and electrolytes to the gut lumen. Marked dehydration, electrolyte abnormalities and associated complications may occur as a result in otherwise well patients. The Therapeutic Goods Administration (TGA) has previously alerted prescribers to the risk of severe electrolyte disturbances in association with the use of sodium picosulfate-containing products (1).

Since January 2002, the TGA has received a total of 51 adverse event reports for these products of which 18 were reports of serious electrolyte disturbances. While it is known that the elderly, the frail and those with cardiac failure or renal impairment are potentially at higher risk of an adverse event, health professionals are reminded that serious adverse events can occur in patients under the age of 60 years who are otherwise fit and healthy, and that this should be considered when prescribing/dispensing these products.

All patients should be reminded of the importance of hydration and electrolyte
replacement while taking these products and to seek medical attention if they experience any signs of severe dehydration, such as excessive thirst, dizziness, confusion and decreased urine output or dark coloured urine. *Extracted from the Medicines Safety Update, Volume 4, Number 1, February 2013 at* http://www.tga.gov.au/safety


### Combined contraceptives: venous and arterial thromboembolism

**European Union** — The European Medicines Agency’s Pharmacovigilance Risk Assessment Committee (PRAC) has formally started a safety review of Diane 35® (cyproterone acetate 2 mg, ethinyloestradiol 35µg), associated names and its generics at its February 2013 meeting.

The Europe-wide review has been initiated at the request of the French medicines regulatory agency (ANSM), following the announcement of its plan to suspend the marketing authorizations for Diane 35® and its generics for acne treatment in France over the next three months. This was the result of an analysis of known data, including reports of venous and arterial thromboembolism recorded in the French national pharmacovigilance database in association with Diane 35® and its generics over a period of more than 20 years.

These medicines have been authorized at the level of individual Member States for many years. They are widely used across Europe. However, their authorized uses differ between Member States. In many countries they are authorized as a contraceptive in women with hormone-related conditions such as acne, hirsutism and alopecia. In France, they are only authorized for the treatment of acne, but ANSM has noted widespread off-label use as a contraceptive.

The risk of venous thromboembolism with these medicines is low but well known and warnings are included in the product information to alert patients and prescribers to the risks. The PRAC will evaluate all available evidence on the benefits and risks of these medicines and give a recommendation on whether marketing authorization should remain as at present, be varied, suspended or revoked, in the interest of all patients in the European Union.

The PRAC has also formally started a review of combined contraceptives containing chlormadinone, desogestrel, dienogest, drospirenone, etonogestrel, gestodene, nomegestrol, norelgestromin and norgestimate, often referred to as third and fourth generation contraceptives.


### Fibrin sealant spray: gas embolism

**European Union** — The European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) has recommended a number of new instructions for healthcare professionals using the fibrin sealants Tisseel®, Tissucol®, Artiss® and Beriplast P® (and associated names) to optimize the safe use of these medicines when applied as spray during surgery.

This follows the CHMP advice on two other fibrin sealants, Evicel® and Quixil®, adopted in November 2012.

Fibrin sealants are used in a wide range of surgical procedures to help reduce local bleeding. They can be applied by dripping or spraying the solution onto bleeding tissue, where they form a fibrin clot, stopping bleeding and thereby helping the wound to heal.
The review of fibrin sealants was initiated following reports of gas embolism with Evicel® and Quixil® in association with the use of spray devices that use a pressure regulator to administer these medicines. These events appear to be related to the use of the spray device at higher-than-recommended pressures and/or in closer-than-recommended proximity to the tissue surface.

The Committee recommended that:

• The product information should be updated with clear and consistent advice for healthcare professionals regarding recommended pressure and distance to use during spraying application.

• Marketing authorization holders for these medicines should ensure that they are used with pressure regulators that do not exceed the maximum pressure required to deliver the fibrin sealant, and that they contain labels stating the recommended pressure and distance.

• The product information should include a warning that the risk of gas embolism appears to be higher when fibrin sealants are sprayed using air, as compared to CO2, and patients should be closely monitored for signs of gas embolism.

• Healthcare professionals in the European Union (EU) will receive a letter outlining the updated information on the safe use of these medicines.

However, for Beriplast P® (and associated names), the CHMP concluded that there is no risk associated with this product because it does not require a gas-assisted spray device during application, therefore there is no risk of gas embolism with this product when used in accordance with prescribing advice and with the recommended device.


Corticosteroids: musculoskeletal adverse events

New Zealand — Healthcare professionals are reminded that corticosteroids are associated with multiple musculoskeletal adverse reactions including avascular necrosis of the bone, osteoporosis and tendinopathies (1).

**Avascular necrosis of the bone** is an uncommon adverse reaction associated with corticosteroids (1, 2). Higher doses of corticosteroids are associated with a greater risk of avascular necrosis even when used for short periods (2). Importantly, avascular necrosis has also been reported with topical application of corticosteroids (3).

**Osteoporosis** is a common adverse reaction associated with long-term corticosteroid treatment, where up to 50% of patients are affected (1, 4). Bone loss is more rapid during the early stages of therapy, is dose-dependent and primarily occurs in trabecular bone (1, 4, 5). Daily doses of greater than 7.5 mg prednisolone (or equivalent) have been associated with a higher risk of fracture than daily doses of less than 2.5 mg prednisolone (or equivalent) (5).

**Tendinopathies** associated with corticosteroid use are predominantly reported in the Achilles and patellar tendons (6). Tendon ruptures have also been reported. Tendinopathies have been associated mainly with oral and intra-articular corticosteroid use (6).

In New Zealand, 40 reports of musculoskeletal adverse events associated with corticosteroids were reported to the Centre for Adverse
Reaction Monitoring (CARM) between January 2000 and June 2012. The majority of the reports were associated with prednisone (30 reports).

The remaining reports were associated with dexamethasone (nine reports), triamcinolone (two reports) and methylprednisolone (one report). In two cases, the patient was on more than one corticosteroid. It is worth noting that in all but one case of tendon rupture the patient was also taking a quinolone antibiotic (7).

The types of musculoskeletal adverse reactions reported in these 40 reports are shown below. Avascular necrosis (55.6%) and osteonecrosis (13.3%) were the most commonly reported musculoskeletal adverse reactions. Of the reported cases of avascular necrosis, two-thirds reported avascular necrosis of the femoral head.

<table>
<thead>
<tr>
<th>CARM reports of musculoskeletal adverse reactions associated with corticosteroids for the period January 2000 to June 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avascular necrosis</td>
</tr>
<tr>
<td>Osteonecrosis</td>
</tr>
<tr>
<td>Tendon rupture</td>
</tr>
<tr>
<td>Myalgia</td>
</tr>
<tr>
<td>Arthritis</td>
</tr>
<tr>
<td>Septic arthritis</td>
</tr>
<tr>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Fracture pathological</td>
</tr>
</tbody>
</table>

Healthcare professionals are encouraged to educate patients about possible adverse reactions associated with corticosteroid use and to ensure treatment and dose is regularly reviewed. Use of more than one medicine with the potential to cause adverse musculoskeletal effects is likely to increase the risk of an adverse reaction, such as avascular necrosis, osteoporosis and tendon disorders.


References


Spontaneous monitoring systems are useful in detecting signals of relatively rare, serious or unexpected adverse drug reactions. A signal is defined as “reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually, more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information”. All signals must be validated before any regulatory decision can be made.
Regulatory Action and News

Herbal medicines: strengthening assessment methodology and improved communication

European Union — In 2012, the European Medicines Agency’s Committee on Herbal Medicinal Products (HMPC) adopted 15 Community herbal monographs and released seven monographs for public consultation. A total of 114 final monographs have been made available since the HMPC was established in 2004.

The monographs published to date cover a large number of therapeutic areas and the work plan of the HMPC for 2013 contains 30 draft or final monographs.

A Community herbal monograph comprises the HMPC’s scientific opinion on a given herbal substance and preparations thereof, based on the evaluation of all available scientific data and information on the historic use of these herbal ingredients in the EU vis-à-vis requirements of the legislation. The information contained in such monographs is used by Member States to support the evaluation of marketing applications from companies.

As part of the 2012–2015 work programme, the HMPC will look into strengthening its assessment methodology and aiming for continued high quality standards for its new or revised assessments. The first monographs having undergone systematic review/revision will be published in 2013.

The Agency has also started working on making the main information contained in the monographs as well as the studies and data used by the HMPC to issue its recommendations more accessible to the general public.

Patient and consumer organizations involved in the Agency’s activities have expressed strong support for this initiative which will represent a valuable source of information on the European view on herbal medicines and add to the vast amount of information released by the different national regulatory authorities on use of herbal medicines resulting from their scientific work within the EU network of medicines agencies.


Advanced therapies: incentives and strengthened interaction

European Union — In 2013, The European Medicines Agency’s Committee for Advanced Therapies (CAT) expects to review three or four marketing authorization applications (MAAs) for advanced-therapy medicinal products (ATMPs). This compares to three applications received in 2012, which led to the authorization for treatment of lipoprotein lipase (LPL) deficiency, a very rare inherited disorder.

While the number of MAAs for advanced therapies is still limited, an analysis of ATMPs under clinical evaluation published in 2012 in the journal Molecular Therapy shows that the research and development pipeline is large. This is confirmed by the amount of scientific advice provided to companies by the CAT and the number of ATMPs which have been classified.

Among the ATMPs under development, three quarters are cell-based medicinal
products while one quarter represents gene therapies. Products are being developed for cancer, cardiovascular diseases and haematology-related conditions.

In December 2012, the Committee published a reflection paper clarifying the legal basis of the classification of medicines as advanced therapies and provides information on how these medicines are classified as gene-therapy, somatic-cell-therapy, tissue-engineered or combined medicines. Some borderline cases and areas where scientific knowledge is limited or evolving rapidly are also discussed.

In 2012, 17 applications were submitted for a scientific recommendation on advanced-therapy classification. The CAT classified 14 of these as ATMPs, compared with the 12 submitted and 12 adopted in 2011. A similar number is expected in 2013.

As part of its work programme 2010–2015, CAT will continue to hold meetings on specific topics with interested parties such as scientific associations or trade organizations.


Methodologies in pharmacovigilance and pharmacoepidemiology

European Union — The PROTECT project, a public-private partnership for innovative methodologies in pharmacovigilance and pharmacoepidemiology, coordinated by the European Medicines Agency (EMA), has reached a crucial stage with the delivery of two databases which will offer access to important data resources for pharmacovigilance activities and pharmacoepidemiological studies.

The first of these two databases, the Drug Consumption Database, is a comprehensive and structured source of information on drug consumption in Europe. It is the result of reviewing, compiling and updating knowledge about European sources of data on drug utilization in out- and in-patient healthcare settings. Information is currently available for 17 EU countries (Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, Latvia, Netherlands, Norway, Poland, Portugal, Spain, Sweden, and United Kingdom) up to October 2012. Work is in progress to expand data.

The second database, the PROTECT ADR database, is a listing of all ADRs contained in section 4.8 of the summary of product characteristics (SmPC) of medicinal products centrally authorized in the EU. It is based on the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The goal of this database is to improve the efficiency of the detection process of ADRs by allowing quick identification and filtering or flagging of listed and unlisted ADR. This database is updated every six months and currently contains information up to 30 June 2012.


Nicotinic acid/laropiprant: suspension recommended

European Union — The European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) has confirmed the recommendation to suspend the marketing authorization for nicotinic acid/laropiprant (Tredaptive®, Pelzont® and Trevaclyn®) used to treat adults with dyslipidaemia. The CHMP decision follows the recent recommendation by
the Pharmacovigilance Risk Assessment Committee (PRAC) to suspend these medicines.

Doctors should no longer prescribe Tredaptive®, Pelzont® or Trewaclyn® and should review patient treatment options.

A review of nicotinic acid/laropiprant was initiated in December 2012 after new data from a large, long-term study called HPS2-THRIVE became available. The results of the study, which are still preliminary, indicated that taking nicotinic acid/laropiprant together with a statin has no significant additional benefit in reducing the risk of major vascular events such as heart attack and stroke, compared with statin-alone therapy. In addition, a higher frequency of non-fatal but serious side effects was seen in patients taking these medicines.


Bevacizumab approved for metastatic colorectal cancer

United States of America — The Food and Drug Administration (FDA) has approved bevacizumab (Avastin®) for use in combination with fluoropyrimidine/irinotecan or fluoropyrimidine/oxaliplatin based chemotherapy for the treatment of patients with metastatic colorectal cancer (mCRC) whose disease has progressed on a first-line bevacizumab-containing regimen. Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that binds to human vascular endothelial growth factor (VEGF), preventing the interaction of VEGF to its receptors on the surface of endothelial cells.

This approval is based on the results of a randomized, open-label, multinational trial enrolling patients with mCRC that progressed during or within three months of discontinuation of bevacizumab-based combination chemotherapy with fluoropyrimidine-oxaliplatin or fluoropyrimidine/irinotecan in the first line. No new safety signals were observed in this trial. The safety data was consistent with the known safety profile established in previously approved indications.


Mercury free healthcare

Health Care Without Harm (HCWH) and the World Health Organization (WHO) are co-leading a global initiative to achieve virtual elimination of mercury-based thermometers and sphygmomanometers over the next decade and their substitution with accurate, economically viable alternatives. This initiative is based on the Mercury in Health Care: 2005 WHO Policy Paper which calls for short, medium and long-term steps to achieve the gradual substitution of mercury-based medical devices.

This project is a component of the UN Environment Programme’s (UNEP) Mercury Products Partnership, which is led by the US Environmental Protection Agency. This broader UNEP Products Partnership seeks action to eliminate mercury in products such as batteries, lighting and lamps, electrical and electronic devices, dental products, and measuring and control devices.

With specific regard to the WHO/HCWH Health Care collaborative initiative, the Products Partnership has set the objective of phasing out, by 2017, the demand for mercury-containing fever thermometers and sphygmomanometers by at least 70% and to shift the production of all mercury-containing fever thermometers and sphygmomanometers to accurate, affordable, and safer non-mercury alternatives.
UNEP has also been charged by the world’s governments to explore the possibility of establishing an international legally binding instrument to address mercury pollution.


Ocriplasmin: approved for vitreomacular traction

European Union — The European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) has recommended marketing authorization for Jetrea®, a medicinal product indicated for the treatment of adults with vitreomacular traction (VMT), an eye condition which can cause severe visual disturbance. This represents the first medicinal option for patients suffering from this condition.

The only active treatment option currently available for VMT is vitrectomy, whereby the vitreous humour is removed. The post-vitrectomy patient may have to undergo a period of four to six weeks without being able to work or live normally, out of which 7 to 14 days may be in a ‘head-down’ position to enhance the success rate of the surgical procedure. This ‘head-down’ posturing can be very inconvenient for the patient, and carries a significant burden of care to family or friends.

Jetrea® contains the new active substance ocriplasmin, a recombinant human protein derived from the yeast Pichia pastoris. Ocriplasmin has enzymatic activity against proteins in the interface between the vitreous humour and the retina. By breaking down these proteins, ocriplasmin can loosen the adhesion between the vitreous humour and the macula and can therefore resolve traction at the macula.


India: clinical trial conditions amended

India — The Ministry of Health has provided rules for granting permission and conducting inspections of clinical trials. Following notification of rules for providing compensation to victims of clinical trials, the Union Health Ministry has now amended the Drugs and Cosmetics (D&C) Rules to set conditions for giving permission to trials and inspection of sites.

The Government issued the notification to add a fresh rule (122 DAC) to the existing guidelines issued by the Drugs Controller General of India (DCGI) which lists all conditions for granting permission for clinical trials.

Schedule Y, requires adherence to good clinical practice guidelines and ethical research committee approval before initiating the study. It also makes trial registration mandatory within the Clinical Trials Registry of India before enrolling subjects. An annual status report of each clinical trial as to whether it is ongoing, completed or terminated must also be submitted to the licensing authority and in case of termination of any clinical trial, the detailed reasons should be communicated.

The notification also stipulates the need for reporting of serious adverse events during trials, rules for medical management of the injury during trials and reporting on compensation provided to victims. It also lays down rules relating to the inspection of sponsor premises, including their employees, subsidiaries, agents, contractors, sub-contractors and trial sites by authorized officers at any time with or
without prior notice. The officers will also have powers to search and seize any record, data, document, books, investigational drugs related to the trials.

The licensing authority may also impose any additional conditions for issuance of permission in respect of specific clinical trials, if considered necessary regarding the objective, design, subject population, subject eligibility, assessments, conduct and treatment of a clinical trial.

Actions that can be taken against the sponsors in the case of non-adherence to the rules are also specified. The licensing authority can repeal permission, debar the investigator and sponsors after giving warning letters in case any discrepancy is found during the inspections.


**eSubmission Gateway release II and eSubmission web client**

**European Union** — The European Medicines Agency’s (EMA) Gateway release II and eSubmission web client are now live for all applications for centralized procedure marketing authorization for human medicines.

Gateway release II is an upgraded version of eSubmission Gateway, the electronic submission channel that the Agency launched in 2012 to allow applicants to submit documents supporting all types of applications for human medicines to the EMA securely over the internet in the Electronic Common Technical Document (eCTD) format. The existing Gateway users will see new features in the system functionality such as an automated confirmation of the technical validation feedback to the applicant and an automated upload to the Agency’s eCTD review system.

As part of this project, the eSubmission web client, which complements the Gateway, is now available as well for applicants with lower transmission volumes. This web-based tool may be more suitable for small and medium-sized companies. Registered applicants can now start submitting all types of centralised procedure eCTD human applications through the web client.

Applicants who have registered and used the web client during the user acceptance testing can continue submitting their applications without further registration from 15 January 2013.

The EMA strongly recommends using Gateway or the web client for all eCTD submissions. Submissions on physical media (CD or DVD) will continue to be accepted as an alternative method for the time being. It is essential that applicants only use one method of submission as duplicate submissions might lead to negative technical validation and cause a delay in the processing of the application.


**United States of America** — The Food and Drug Administration (FDA) has expanded the approved use of Deferasirox (Exjade®) to treat patients aged 10 years and older for chronic iron overload in non-transfusion-dependent thalassaemia (NTDT).

NTDT is a milder form of thalassaemia that does not require individuals to get frequent red blood cell transfusions. However, over time, some patients with NTDT are still at risk for iron overload that damage vital organs.
The FDA is also authorizing marketing of FerriScan® as an imaging companion diagnostic for Exjade® therapy in patients with NTDT. The agency previously cleared FerriScan® for measuring liver iron concentration (LIC), but its use in Exjade® clinical studies to select patients for therapy, and to manage therapy, defined its role as a necessary imaging companion diagnostic. FerriScan® measures LIC non-invasively using magnetic resonance imaging.

Exjade® was previously approved for treatment of chronic iron overload due to blood transfusions in patients aged 2 years and older.


Pomalidomide approved for advanced multiple myeloma

United States of America — The Food and Drug Administration (FDA) has approved pomalidomide (Pomalyst®) to treat patients with multiple myeloma whose disease progressed after being treated with other cancer drugs.

Pomalyst® is intended for patients who have received at least two prior therapies, including lenalidomide and bortezomib, and whose disease did not respond to treatment and progressed within 60 days of the last treatment.

Pomalyst carries a boxed warning that the drug should not be used in pregnant women because it can cause severe life-threatening birth defects, and that the drug can cause blood clots. Because of the embryo-fetal risk, it is available only through the Pomalyst® Risk Evaluation and Mitigation Strategy (REMS) Programme.

Common side effects include neutropenia, anaemia, constipation, diarrhoea, thrombocytopenia, upper respiratory tract infections, back pain and fever.


Nalmefene approved for reduction of alcohol consumption

European Union — The European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) has recommended the granting of a marketing authorization for nalmefene (Selincro®), a medicinal product intended for the reduction of alcohol consumption in adults with alcohol dependence. Nalmefene is an opioid receptor antagonist.

Selincro® is indicated to help lower alcohol consumption in adults with alcohol dependence who have a consumption of more than 60 g of alcohol per day for males, and more than 40 g of alcohol per day for females, who do not have physical withdrawal symptoms and who do not require immediate detoxification.

The Committee also recommended that Selincro® should be prescribed in conjunction with continuous psychosocial support that focuses on treatment adherence and reducing alcohol consumption. The medicine should only be prescribed to patients who continue to have a high drinking risk level two weeks after initial assessment.


Mipomersen sodium and lomitapide approved for inherited cholesterol disorder

United States of America — The Food and Drug Administration has approved mipomersen sodium (Kynamro®) injection as an addition to lipid-lowering
medications and diet to treat patients with homozygous familial hypercholesterolemia (HoFH). The addition of Kynamro® helps to reduce low-density lipoprotein-cholesterol (LDL-C), apolipoprotein B, total cholesterol, and non-high density lipoprotein-cholesterol (non HDL-C).

In December 2012, the FDA also approved lomitapide (Juxtapid®) to reduce LDL-C, total cholesterol, apolipoprotein B, and non HDL-C in patients with HoFH.

HoFH, an inherited condition that occurs when the body is unable to remove LDL-C from the blood causing abnormally high levels of circulating LDL-C. For those with HoFH, heart attacks and death often occur before age 30.

The most common adverse reactions in the clinical trial included injection site reactions, flu-like symptoms, nausea, headache and serum transaminases.


Imatinib mesilate: marketing authorization application withdrawal

European Union — The European Medicines Agency (EMA) has been notified by the manufacturer of its decision to withdraw its application for centralized marketing authorization for the medicine imatinib mesilate (Ruvise®), 100- and 400-mg film-coated tablets. It was intended to be used for adults as add-on therapy for the treatment of pulmonary arterial hypertension (PAH).

The company has withdrawn the application since additional data are required to address CHMP questions relating to the benefit-risk assessment of imatinib in PAH patients. These data will not be available within the time-frame allowed in the centralized procedure.


Memantine: Imatinib mesilate: marketing authorization application withdrawal

European Union — The European Medicines Agency (EMA) has been notified by the manufacturer of its decision to withdraw its application for the medicine memantine (Memantine FGK®), 7 mg, 14 mg, 21 mg and 28 mg, prolonged-release hard capsule. It was intended to be used for the treatment of patients with moderate to severe Alzheimer disease.

In its letter, the company stated that it is withdrawing the application for strategic reasons.

Recent Publications, Information and Events

WHO/WIPO/WTO: health innovation and access to medicines

For the first time, the three global intergovernmental bodies dealing with health, intellectual property and trade have pool-ed their expertise on a study of policies needed to advance medical and health technologies and to ensure they reach the people who need them.

Promoting access to medical technologies and innovation: intersections between public health, intellectual property and trade was launched by the World Health Organization (WHO), World Intellectual Property Organization (WIPO) and World Trade Organization (WTO).

Public health remains a clear imperative for the international community, and promoting both medical innovation and access to the fruits of that innovation is indispensable for progress towards improved and more equitable health outcomes. But to achieve this result demands greater practical cooperation and dialogue within the international system.

The book covers a broad range of complex, yet linked issues relating to public health and innovation in medical technologies, with the ultimate goal of accessibility — making medical advances available globally to all who are sick. It provides solid information for anyone concerned with these issues.

Its target audiences are policymakers, legislators, government officials, delegates to international organizations, nongovernmental organizations, and researchers. The study reflects the debate about health that has evolved over the years, with increasing attention given to medical technologies and their invention and dissemination. Public health and innovation policies, and the rules of trade, competition and procurement, all play a part.

The policy-making focus has broadened from the basic questions of ensuring access to essential medicines, and developing treatments for neglected diseases that are available and affordable for those who are primarily affected — the poor. This is part of the right to health.

More recently, attention has turned to other aspects of how to meet this right: including the measures that are needed to provide incentives for medical innovation — such as medicines, vaccines and medical devices — and how to ensure equitable access to all of these vital medical technologies.

Part of the picture is the international patent system and how governments implement it domestically according to the needs of their countries. The patent system is designed to support innovation, and offers a mechanism to ensure that these innovations are accessible to society.

The research and development pharmaceutical industry therefore relies heavily on exclusive patent rights in order to recoup the investment made in research and development, as shown by the high number of applications for patents on medical technologies under WIPO’s Patent Cooperation Treaty.

The secretariats of the three organizations have drawn on their experience and the data available to them to produce
this study and to support discussions on policy options and legal issues.

The book looks at the need for international cooperation, who is involved, and how to address the challenges that the sector is facing. It examines in detail the range of policy issues from health and human rights and national, regional and global regulation policies, to intellectual property, trade and tariffs, procurement, free trade agreements and other aspects of policy.

It studies a range of issues, such as patents in the pharmaceutical sector; traditional medical knowledge, the importance of knowing what is patented and where, and how easy it is to find out, and questions of affordability and availability of medicines and market failure.

It looks at the development of medical technologies, modern research and development, ways of providing incentives for innovation, and ways of dealing with market failures, in particular with new products for treating neglected diseases. It also includes comprehensive sections on trade and intellectual property rules and the flexibilities they contain for governments to meet various public health objectives.

Reference: World Health Organization (WHO), World Intellectual Property Organization (WIPO) and World Trade Organization (WTO). Promoting access to medical technologies and innovation: intersections between public health, intellectual property and trade. Available from WHO Press at bookorders@who.int

EPN study: availability and pricing of children’s medicines in Ghana

The continuous availability of affordable medicines for children is necessary for countries to reduce infant mortality, in keeping with Millennium Development Goal (MDG) 4. In recognition of the importance of availability of medicines for children to the success of MDG 4, the World Health Assembly passed Resolution WHA60.20 in 2007, to include essential children’s medicines in national medicine lists, procurement and reimbursement schemes.

In January 2011, the Ecumenical Pharmaceutical Network (EPN) conducted a study to determine the availability and pricing of selected essential medicines for children in church health facilities in Ghana. The EPN study followed up on a 2007 World Health Organization (WHO) survey of children’s medicines availability in 14 African capitals, which had revealed poor availability of medicines for children in both public and private facilities.

This study was the first significant attempt to collect data on the availability of children’s medicines in health facilities in Ghana. Previous studies have focused on the availability of medicines in general, or on all health facilities, with no focus on either children’s medicines or faith-based health facilities. A similar study was carried out by EPN in Chad, Kenya and Uganda.

Results of the study show that zinc sulphate, chlorpheniramine syrup and vitamin A had the lowest availabilities and over 40% of the facilities surveyed were not stocking zinc sulphate dispersible tablets, vitamin A capsules and chlorpheniramine syrup at all. Unavailability of these crucial medicines could largely compromise the quality of healthcare offered to children.


IOM report on substandard and falsified medicines

The US Institute of Medicine (part of the American Academies of Science) has published a report on Countering the pro-
blem of falsified and substandard drugs. The very careful development and review process of IOM reports is comparable to that of WHO Expert Committee reports.

The report identifies, in particular, the distinction between substandard, falsified and counterfeit medicines. This is a very helpful approach to enabling a meaningful discussion. The report then focuses on the public health impact of substandard and falsified medicines while the term counterfeit medicines is reserved for trade-mark infringements, which are considered outside the scope of the report. Chapter three of the report contains a comprehensive overview of the extent of the problem of substandard and falsified medicines.

The report also makes a number of recommendations for the Food and Drug Administration (FDA), who commissioned the report, and for national authorities, covering various ways and means to strengthen regulatory oversight and to promote supply chain security. For example, a three-step approach is recommended, starting with registration/licensing of all medicine importers in a country, followed by registration/licensing of all national institutions that buy/sell medicines (secondary wholesalers, pharmacies, etc.) and ultimately the use of unique identifiers of individual packages as a final step. This approach is in line with recent EU directives coming into force.

The report also proposes the development of an international code of practice. This type of non-binding international rule would identify and promote regulatory and other governance measures that have proven to be effective in containing substandard and falsified medicines, and could serve as an action guide.


HIFA: Information for healthcare providers

Access to reliable, unbiased information on medicines is fundamental to healthcare. Prescribers and users often lack such information, especially in low-resource settings. Some have no information at all, or the information that they do have is commercially biased. As a result, countless people suffer harm, and sometimes death, as a result of prescribing errors such as the wrong medicine, or the wrong dose. Furthermore, irrational prescribing promotes the emergence of drug resistance. Countless people are already dying from multidrug-resistant tuberculosis and other drug-resistant strains that have emerged largely because of irrational prescribing. There is a real and growing threat to the human species from new microbes that are resistant to all known treatments.

Each year, Healthcare Information for All (HIFA) includes a focus on a specific group of healthcare providers. The HIFA Steering Group has announced the focus of the HIFA 2013–15 challenge to be Meeting the information needs of prescribers and users of medicines. A new page on the HIFA website has been created for this purpose at http://www.hifa2015.org/2013-15-challenge-prescribers-and-users-of-medicines/

The HIFA vision is that every prescriber and user of medicines will have access to the information and knowledge they need to use medicines effectively. HIFA is bringing together a working-group of volunteers to take this forward. The group will:

• Promote discussion on HIFA2015 on relevant issues, including drivers and barriers to the availability and use of reliable information on medicines.
• Promote discussion on issues that are particularly relevant to different groups of prescribers and users.
pregnant women coming for care but also enables later comparison of birth defects among women who have been exposed to a medicine with those who have not. The second feature is the generic applicability of the approach irrespective of drug or disease, and the third is the improvement of staff capacity to manage and monitor pregnancies and newborns. These qualities add to the practicality and cost-effectiveness of the protocol.

The materials developed are available to any country wishing to join the WHO Pregnancy Registry, on condition that there is a commitment to train the staff to use the materials, to obtain reliable data on drug exposure and to conduct a systematic surface examination of the newborn. The Registry builds capacity within the health system to improve maternal and neonatal care as well as to serve as a sentinel surveillance system for the safety of medicines used in pregnant women.

The specific objectives of the WHO Pregnancy Registry are to:

- Build capacity to obtain reliable information on obstetric, medical, and drug history during pregnancy and diagnose, assess, monitor and manage pregnancy and the outcomes of pregnancy including congenital malformations, stillbirths and prematurity.
- Quantify the baseline risk of major congenital malformations in the absence of drug exposure during the course of pregnancy.
- Quantify the risk of major congenital malformations associated with exposure to medicines during the course of pregnancy.
- Identify other obstetric, therapeutic and clinical factors that may contribute to the risk of major congenital anomalies and other adverse birth outcomes in pregnant women.

New pregnancy registry protocol

A new protocol has been published in *BMC Pregnancy and Childbirth* for collecting data on the risks of birth defects due to medicines for diseases such as HIV and malaria. The major components of first-line treatments for these diseases are not recommended during the first trimester, yet many women may take these medications before they are aware that they are pregnant. Sixty-eight percent of the world’s HIV population reside in sub-Saharan Africa and approximately 25 million pregnant women are at risk of malaria.

The protocol is neither disease nor drug-specific. The power of the approach lies in its broad application to a variety of settings in which women may have more than one infectious disease or condition during the course of pregnancy and may also have been exposed to many drugs. Its methods, case record forms and training materials (including a DVD showing how to conduct a surface examination of a newborn) have been tested for feasibility in five countries (four in Africa and one in South America), and further refined and used in the WHO Pregnancy Registry. The approach is integrated within the reproductive health system of the countries, specifically antenatal clinics and labour/delivery facilities.

There are three important features of the pregnancy registry protocol which stand out from most other registries. The first is the simplicity of including women agreeing to take part at their first facility visit for care during their pregnancy. This not only represents the population of pregnant women coming for care but also enables later comparison of birth defects among women who have been exposed to a medicine with those who have not. The second feature is the generic applicability of the approach irrespective of drug or disease, and the third is the improvement of staff capacity to manage and monitor pregnancies and newborns. These qualities add to the practicality and cost-effectiveness of the protocol.

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- Quantify the risk of major congenital malformations associated with exposure to medicines during the course of pregnancy.
- Identify other obstetric, therapeutic and clinical factors that may contribute to the risk of major congenital anomalies and other adverse birth outcomes in pregnant women.
• Support a culture of drug safety awareness among women and their providers in participating countries and avoid preventable adverse drug-related pregnancy outcomes.

• Develop an ongoing surveillance system of maternal and newborn health that strengthens the health system to improve maternal and neonatal outcomes.

Reference: Special Programme for Research and Training in Tropical Diseases. TDR eNewsletter, December 2012 at http://www.who.int/tdr

Malaria: rapid diagnostic testing

Malaria rapid diagnostic test performance is the fourth report in a series of laboratory-based evaluations of rapid diagnostic tests (RDTs) for malaria. It provides a comparative measure of their performance in a standardized way to distinguish between well and poorly performing tests. This information can be used by malaria control programmes and to guide UN procurement policy for these diagnostic tools.

In Round 4, 48 products were evaluated. Overall, the majority of resubmitted products either maintained or improved their performance in Round 4, indicating product improvement by the manufacturers. Also included in the report is an algorithm to assist in the RDT selection process, a field tool to assess RDT packaging, safety and ease-of-use, and a pictorial guide to common anomalies seen in production lots.

The evaluation programme is co-sponsored by the Foundation for Innovative New Diagnostics (FIND), the Special Programme for Research and Training in Tropical Diseases (TDR) and the WHO Global Malaria Programme (GMP). Testing is performed at the US Centers for Disease Control and Prevention (CDC).


Paediatric ACTs for the treatment of uncomplicated malaria

The Medicines for Malaria Venture (MMV) has announced the release of a new independent study focused on assessing critical barriers to the acceptance and uptake of quality antimalarial medicines for children.

The study examines six francophone countries in Central and West Africa, and draws on a WHO-endorsed framework for evaluating barriers to access to essential medicines. It suggests interventions that could enhance acceptance and uptake of WHO-recommended medicines for children.


International course on dengue

The 13th International Course on Dengue will be held 12–23 August 2013 in Havana, Cuba. Through theoretical and practical sessions, the main aspects related to dengue will be covered: dengue epidemiology, clinical management, diagnosis, virology and immunology, vector control, environmental risk factors and community participation.

Important aspects to be discussed are trends of dengue at global level, impact of climate change, new dengue clinical classification, opportunities for diagnosis, impact of virus diversity, immunogenetics, complexity of dengue immunity and pathogenesis, dengue vaccines, integrated surveillance and control, difficulties, options, challenges, economic burden, new options for control, and insecticide resistance, among others.
The new global initiatives for dengue and the experiences of several countries and geographical regions will also be updated and general lectures as well as round tables and symposia are scheduled. Two mini-courses on GIS and dengue and modeling of transmission and prediction of dengue as well as other activities and meetings will be also organized.

The course is provided by the PAHO/WHO Collaborating Centre for the Study of Dengue and its Vector, Pedro Kourí Tropical Medicine Institute, Havana, Cuba, in collaboration with the Cuban Ministry of Public Health, the Cuban Society of Microbiology and Parasitology and the Pan American Health Organization (PAHO).

4. Reference Substances and Reference Spectra

Draft proposal for the Supplementary Information section of *The International Pharmacopoeia* (January 2013). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland or e-mail to Schmidth@who.int. Working documents are available for comment at http://www.who.int/medicines.

[Note from the Secretariat: *The Supplementary Information section of The International Pharmacopoeia provides the user with texts for guidance and information and will not constitute part of the standards.*]

4.1 International Chemical Reference Substances

4.1.1 Introduction

International Chemical Reference Substances (ICRS) are primary chemical reference substances for use in physical and chemical tests and assays described in *The International Pharmacopoeia* or in other World Health Organization (WHO) quality assurance documents adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations. ICRS are used to identify, determine the purity or assay pharmaceutical substances and preparations or to verify the performance of test methods.

This chapter describes principles to be applied during the establishment and use of ICRS, which guarantee that the reference substances are suitable for their intended purpose.

This chapter is not applicable to WHO International Biological Reference Preparations.

4.1.2 Terminology

Chemical reference substance

The term chemical reference substance, as used in this text, refers to an authenticated, uniform material that is intended for use in specified chemical and physical tests, in which its properties are compared with those of the product under examination and which possesses a degree of purity adequate for its intended use.

Primary chemical reference substance

A designated primary chemical reference substance is one that is widely acknowledged to have the appropriate qualities within a specified context and whose assigned content when used as an assay standard is accepted without requiring comparison with another chemical substance.
Secondary chemical reference substance
A secondary chemical reference substance is a substance whose characteristics are assigned and/or calibrated by comparison with a primary chemical reference substance.

4.1.3 Purpose of ICRS

The purpose of establishing ICRS is to provide users of The International Pharmacopoeia or other WHO quality assurance documents adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations with authenticated substances for reference. Many analytical tests and assays are based on comparison of physical or chemical properties of a sample with those of a reference standard. ICRS serve as such reference standards and thus enable the analyst to achieve accurate and traceable results. Furthermore ICRS may be used to assess system suitability during analyses and to calibrate analytical instruments.

ICRS may also be employed to establish secondary reference substances according to the WHO General guidelines for the establishment, maintenance and distribution of chemical reference substances. In cases of doubtful results or dispute, however, the tests performed using ICRS are the only authoritative ones.

4.1.4 Establishment of ICRS

All operations related to the establishment and distribution of ICRS should be carried out according to the relevant guidelines. Among these, the WHO General guidelines for the establishment, maintenance and distribution of chemical reference substances and International Organization for Standardization (ISO) Guide 34 – General requirements for the competence of reference material producers (including related guides) have a prominent position.

Production

Source material for the establishment of ICRS may be synthesized and purified for this purpose or may be selected from the regular pharmaceutical production of the monographed substance provided that the purity and homogeneity are suitable. In some cases, for example, in order to improve the stability of the reference substance, it may be useful to select an alternative salt (or salt vs base), solvate or hydrate. The content assigned to the standard takes into account which substance is selected.

Compliance with the relevant tests of the corresponding monograph as published in The International Pharmacopoeia is required where applicable.

Reference standards are dispensed into suitable containers under appropriate filling and closure conditions, to ensure the integrity of the reference material. The containers employed are preferably single-use in order to minimize the risk of decomposition, contamination and moisture uptake. Where multiple-use containers are employed appropriate use and handling controls should be implemented to assure their suitability.

WHO encourages pharmaceutical manufacturers to donate suitable candidate materials and thus to contribute to the availability of ICRS.
Analytical characterization

The source material should be tested with suitable analytical techniques aiming to characterize all relevant quality attributes. The identity is confirmed and the purity is determined, usually based on results obtained with the validated methods of the respective monographs. However, the use of further analytical techniques may be appropriate in order to fully characterize the candidate material. Absolute methods (for example, volumetric titrations, differential scanning calorimetry) should be employed to complement and verify the results of relative methods where the properties of a sample are compared with those of a reference substance (for example, chromatographic methods). The extent of testing and the number of laboratories involved in characterizing the material depends on the intended use of the reference substance to be established. If required, assay standards are characterized in interlaboratory trials to increase the accuracy of the assigned value and to determine the associated uncertainty.

A thorough purity investigation is usually performed with the aim to identify and quantify all components of the candidate material (i.e., main component, organic and inorganic impurities, water and residual solvents). The elucidation of the composition of the candidate material is usually considered as accomplished when all components have been identified and quantified, if relevant. The cumulative percentage of all components should yield 100% (mass balance approach).

The purity of a candidate material is usually calculated on the “as is” basis, so that the analyst can use the substance without pretreatment, for example, drying.

Provided that all components themselves are expressed as a percentage of the weight of sample taken the “as is” content can be calculated as follows:

\[
purity = 100 - \text{organic impurities}\% - \text{inorganic impurities}\% - \text{water}\% - \text{residual solvent}\%
\]

When chromatographic methods are used to test for related substances impurity concentrations are often determined in relation to the principal compound. The “as is” content of organic impurities, to be substituted in the formula above, can be calculated as follows:

\[
\text{organic impurities}\% = \text{chromatographic result} \times \frac{(100 - \text{water}\% - \text{residual solvent}\% - \text{inorganic impurities}\%)}{100}
\]

The content assigned to a quantitative ICRS depends on the purity of the candidate material and on the selectivity of the method for which the standard will serve as a reference. If the standard is intended to be used with a method that has the same selectivity than the method used to determine its purity the calculated purity will be assigned as the content of the ICRS. However, if the intended method is less discriminative, it may be necessary to add to the purity the content of impurities that cannot be discriminated from the response of the parent compound. The following example illustrates this:

A candidate material is analysed with different analytical methods to identify and quantify all relevant components. The results reveal that, besides the labelled sub-
tance, the following components are present: 2.0% water (analysed by Karl Fischer titration, calculated on an “as is” basis); 1.0% enantiomer of the labelled substance (analysed by chiral HPLC, calculated in relation to the sum of the peak areas of both enantiomers); and two organic impurities, each 0.75% (analysed by an achiral HPLC method, calculated in relation to the sum of the peak area of all peaks, ignoring solvent and injection peaks). The purity of the standard is calculated to 95.55% (purity = 100% – (2.5% x 0.98) – 2%). The candidate material is intended to be used as a reference in an assay test, which stipulates the use of the same HPLC method as already applied to determine the organic impurities in the characterization of the candidate material. A content of 96.53% is assigned to the reference substance (assigned content = 100% – (1.5% x 0.98) – 2%). The concentration of the enantiomer is not taken into consideration as the method, for which the reference substance is intended, is not selective for the enantiomer.

Labelling: The labelling should provide all information necessary to use the reference substance as intended, i.e. the name of the reference substance, the batch number, storage conditions, etc. If intended for quantification the assigned content or potency (for microbiological assays) is also given. The accompanying leaflet is considered to be part of the labelling.

Release and adoption
ICRS are established and released under the authority of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. The Committee adopts new ICRS and new lots as being suitable for use as described in The International Pharmacopoeia or in other WHO quality assurance documents.

Stability monitoring and distribution
At the WHO custodian centre for ICRS the established reference substances are stored and distributed under conditions suitable to ensure their stability.

The stability of ICRS is monitored by regular re-examinations. Their frequency and extent is based on the:

- liability of the ICRS to degradation
- container and closure system
- storage conditions
- hygroscopicity
- physical form
- intended use

The analytical methods employed to verify the stability are often chosen among those performed during the establishment of the reference standard. The maximum permitted deviation from the assigned value should be predefined and, if exceeded, the batch should be re-established or replaced.

4.1.5 Use and storage of ICRS by the user

The letters RS after the name of a substance in a test or assay described in The International Pharmacopoeia or in other WHO quality assurance documents adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations indicate the use of the respective ICRS.
ICRS are suitable for the analytical purpose described in *The International Pharmacopoeia* or other WHO quality assurance documents adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations. Directions for use of ICRS are also given in the leaflet enclosed with the substance when distributed. When used for other purposes the responsibility for assessing the suitability rests with the user or the authority that prescribes or authorizes this use. If reference standards other than ICRS are used for purposes described in *The International Pharmacopoeia* or in other WHO quality assurance documents adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations the suitability of these substances has to be demonstrated by the user.

The user has to consider an assigned content in assay determinations or when it is indicated in the method description.

ICRS are supplied in adequate quantities for immediate use after opening of the container. Users should purchase only sufficient amount for short-term use.

It is generally recommended that the user stores ICRS protected from light and moisture and preferably at a temperature of about 5 ± 3 °C. When special storage conditions are required this is stated on the label or in the accompanying leaflet.

If an unopened container is stored under the recommended conditions it remains suitable for use as long as the respective batch is valid. Information on current batch numbers is provided on the web site of the WHO custodian centre for ICRS (see under ordering information).

Reference standards that are normally stored at 5 ± 3 °C are dispatched at ambient temperature since short-term excursions from the storage recommendations are considered not deleterious to the reference standard. Reference standards stored at -20 °C are packed on ice or dry ice and dispatched by courier. Reference standards stored at -80 °C or stored under liquid nitrogen are packed on dry ice and dispatched by courier.

### 4.1.6 Ordering information

Since April 2010 the European Directorate for the Quality of Medicines and Health-Care (EDQM), Council of Europe, is responsible for the establishment, preparation, storage and distribution of ICRS for *The International Pharmacopoeia*. A list of ICRS currently available can be found on their web site (see http://www.edqm.eu).

Orders for International Chemical Reference Substances should be sent to:

European Directorate for the Quality of Medicines & HealthCare  
7 allée Kastner  
CS 30026  
F-67081 Strasbourg  
France  
Fax: +33 (0)3 88 41 27 71 — to the attention of EDQM Sales Section  
E-mail: orders@edqm.eu

The current price for ICRS is 70 Euros per package. Extra charges will be added for the delivery of the reference substances. For details see the above-mentioned web site.
The WHO International Standard for endotoxin is available from the National Institute for Biological Standards and Control (NIBSC).

National Institute for Biological Standards and Control
Blanche Lane
South Mimms
Potters Bar
GB-Hertfordshire EN6 3QG
United Kingdom of Great Britain

4.2 International Infrared Reference Spectra

International Infrared Reference Spectra (IIRS) are provided for use in identification tests as described in monographs of The International Pharmacopoeia or other WHO quality assurance documents adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations.

The reference spectra are produced from authenticated material using an appropriate sample preparation technique. They are recorded with a Fourier transform infrared spectrophotometer (FTIR). Instructions for the preparation of spectra are given in 1.7 Spectrophotometry in the infrared region; Identification by reference spectrum. A spectrum of the test substance is considered to be concordant with a reference spectrum if the transmission minima (absorption maxima) of the principal bands in the test spectrum correspond in position, relative intensities and shape to those in the reference spectrum.