

WHO Drug Information

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WHO Prequalification of Medicines Programme

Facts and figures for 2010

Evaluation of medicines by the WHO Prequalification of Medicines Programme (PQP) includes assessment of data and information on safety, efficacy and quality. Inspections are performed to assess compliance with good manufacturing practices (GMP) and include manufacturers of selected active pharmaceutical ingredients (API) and clinical sites. Clinical sites, including contract research organizations (CROs), are also inspected to verify bio-equivalence with good laboratory practices and good clinical practices.

Thirty-six products were prequalified in 2010, of which 30 were generics. At the end of 2010, the WHO list of prequalified medicines totalled 252 products manufactured in 20 countries. WHO prequalification "firsts" included artesunate powder for injection (which was the first prequalified sterile product made in China); the first combination tenofovir disoproxil fumarate/lamivudine and the first generic emtricitabine.

Six medicines quality control laboratories (QCLs) were also prequalified: one in Bolivia, one in Canada, one in Peru, two in Ukraine and one in Uruguay. At the end of 2010, a total of 17 QCLs had been prequalified and a further 30 were working towards becoming prequalified.

Invitations to manufacturers to submit an expression of interest (EOI) for product evaluation were issued for anti-TB medicines, HIV/AIDS-related care and treatment products, and reproductive health products. The new invitations incorporate additional products and/or take into account revisions made to WHO treat-

ment guidelines. Additionally, the first invitation to manufacturers of active pharmaceutical ingredients (APIs) was issued in October 2010, marking the launch of WHO prequalification of APIs. (A second, expanded invitation to API manufacturers to submit an EOI was issued in March 2011.) It is expected that time taken to reach prequalification will be shorter for finished pharmaceutical products (FPPs) that are manufactured using WHO-prequalified APIs, than for FPPs that are manufactured using APIs that have not previously been evaluated by WHO PQP.

Assessment activities

In 2010, 51 dossiers were submitted and 53 dossiers (two of which were received in late 2009) were accepted for evaluation. Nearly 1000 assessment reports were produced. PQP also assessed nearly 600 variations submitted by manufacturers of prequalified products.

The assessment sessions held in Copenhagen, Denmark, include a training component which is enabling a growing number of developing country assessors to acquire stringent regulatory expertise. The Copenhagen sessions also incorporate technical consultations so that applicants can discuss technical issues relating to their dossiers with assessors. The consultations benefit from the presence of a range of assessors with considerable assessment experience.

A new collaborative procedure for facilitating registration of prequalified medicines in the East African Community (EAC) was piloted. The overall aim was to identify a framework, for WHO-EAC, for joint evaluation and approval of dossiers and

inspections of medicine manufacturing sites, and to ensure that these assessments are integrated into national regulatory decision-making. Two assessors each from three EAC countries (Kenya, Tanzania and Uganda) and six WHO assessors jointly assessed two product dossiers submitted by a single manufacturer. The dossiers were submitted in parallel, and with identical content, to each participating EAC country and to PQP. The products were both prequalified: HA488 (abacavir, dispersible tablets 60 mg) in August 2010 and TB217 (amikacin, injection 500 mg/2 ml) in January 2011. For the manufacturer, the principal benefit of this joint assessment was that once the products had been jointly assessed and approved by WHO-EAC, they were granted immediate access to the markets of each of the countries that had participated in the joint assessment. For the regulators involved, such joint assessment contributes to harmonization of regulatory requirements at regional level. PQP is hoping to use the same model for assessing selected, technically complex, high-priority products. Several partners and stakeholders see joint assessment as an effective means of speeding up access to much needed products.

Inspections

PQP inspectors carried out 59 inspections in 18 countries: 38 of finished pharmaceutical product manufacturing sites; five of API manufacturing sites; seven of CROs and nine of pharmaceutical QCLs. (Inspections were carried out mostly in India and in China, but also in Algeria, Belgium, Bolivia, Egypt, France, Iran, Kenya, Morocco, the Netherlands, Peru, Russia, South Africa, Tanzania, Uganda, Uruguay, the United States and Zimbabwe.)

A new collaborative procedure for joint inspections was initiated at the beginning of 2010. A secure web site has been established for the sharing of inspection

plans, arranging of joint inspections, and sharing of information and inspection reports, with recognition by participating EAC parties and PQP. This will be further explored and possibly expanded. Joint inspections are planned for 2011 in an attempt to prevent duplication of inspections. Inspection reports will be shared by the parties following the inspection. It is hoped that the outcome of the inspection will be accepted by all participating inspectorates. PQP continues to invite local medicines regulatory authority staff or observers to participate in inspections.

The risk assessment procedure for identifying which API manufacturing sites should be inspected has been completed for substances used to manufacture products for the treatment of malaria and TB. It is planned to expand this risk assessment to APIs used in products for the treatment of HIV/AIDS.

Advice and assistance

PQP continues to respond to manufacturers' request for assistance concerning issues relating to, for example, bioequivalence study protocols and choice of comparator products.

PQP continues to provide technical assistance to manufacturers and national QCLs that aims at resolving specific practical problems related to GMP, good practices for QCLs and/or meeting medicines regulatory requirements. Assistance is given in the form of an audit, advice on development of an improvement plan, and training in technical or regulatory areas. Follow-up missions are also organized to support implementation of improvement plans. In 2010, PQP organized 22 technical assistance missions to pharmaceutical manufacturers in four countries (Argentina, China, India and Indonesia) and 10 technical assistance missions to national QCLs (in Argentina, Brazil, Burkina Faso, China, Egypt, Jamaica, Panama, Peru and Yemen).

Training and hands-on practice remain crucial to capacity building. PQP organized, co-organized or supported 23 training courses. Training on general or specific technical issues was given to manufacturers, and to MRA and QCL staff, as well as an introduction and/or update on PQP requirements and services. Training included group sessions as well as discussion sessions with members of assessment or inspection teams working with PQP. In 2010, these workshops involved more than 1200 participants representing regulatory authorities, pharmaceutical manufacturers and QCL staff.

Testing of medicines quality

When implementing sampling and testing projects PQP evaluates specifically the quality of WHO-prequalified products. In a study of the quality of antimalarials, concluded in 2010, the quality of WHO-prequalified products far exceeded that of non-WHO-prequalified products. (Less than 4% of WHO-prequalified artemether-lumefantrine and artesunate-amodiaquine samples failed to comply with international quality standards, whereas the failure rate reached 60% for non-WHO-prequalified samples of the same composition.) Similarly, a survey of the quality of anti-TB medicines conducted in 2009/2010 in Armenia, Azerbaijan, Belarus, Kazakhstan, Ukraine and Uzbekistan showed that all prequalified products sampled and containing isoniazid/ri-fampicin complied with international quality standards.

Norms and standards underpinning or relevant to WHO prequalification activities

The Forty-fifth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations adopted five monographs for HIV and related conditions, four monographs for antimalarial medicines, six monographs for

antituberculosis medicines, two monographs for influenza-specific antiviral medicines and one for a reproductive health product. The Committee also adopted a number of new or revised guidelines and procedures of direct relevance to PQP's activities.

Improving PQP services

The results of a survey of manufacturers provided further information for developing greater "client" focus. Based on the survey results, PQP staff worked on improvements to the Programme, some of which have already been implemented. For example, raising awareness of the opportunity for manufacturers to meet and consult with PQP assessors, clarifying procedure for resolving disagreements surrounding questions raised during the assessment of product dossiers — and some of which (e.g., reducing the time taken to review and reply to applicants during the dossier assessment process, providing the same assessors throughout the assessment process for a product dossier) depend upon completion of other activities (e.g., finalization of PQP's new information management system). Others — for example, the perceived greater stringency of WHO GMP requirements — will require further discussion with manufacturers.

Benefits to manufacturers

In 2010, PQP initiated a study to help it describe and quantify the potential benefits to manufacturers of having a product or products prequalified by WHO. PQP will use the results to develop a "business case for participation in WHO medicines prequalification" for presentation to manufacturers.

Further information on the WHO Prequalification of Medicines Programme, including the full list of medicines prequalified by WHO can be found at: <http://www.who.int/prequal>.

Safety and Efficacy Issues

Safety trials for long acting beta-agonists

United States of America — To further evaluate the safety of long acting beta-agonists (LABAs) when used in combination with inhaled corticosteroids for the treatment of asthma, the Food and Drug Administration (FDA) is requiring manufacturers to conduct five randomized, double-blind, controlled clinical trials comparing the addition of LABAs to inhaled corticosteroids versus inhaled corticosteroids alone.

Four clinical trials will be conducted in adult and adolescent patients 12 years of age and older to evaluate:

- Budesonide and formoterol.
- Fluticasone and salmeterol.
- Mometasone and formoterol.
- Formoterol.

One clinical trial will be conducted in paediatric patients aged 4 to 11 years and will include 6200 patients. Patients in all trials will be treated for six months, and the primary endpoint will be a composite of serious asthma outcomes: asthma-related death, intubation, or hospitalization. The paediatric trial will also assess other relevant quality of life endpoints such as days of school missed and emergency room visits because of asthma related illness.

The clinical trials will begin in 2011 and FDA expects to receive results in 2017.

Reference: *FDA Drug Safety Communication*, 15 April 2011 at <http://www.fda.gov/Drugs/DrugSafety>

Rotavirus vaccination: risk of intussusception

Australia — The Therapeutic Goods Administration (TGA) has undertaken an investigation of a possible association between the use of the rotavirus vaccines Rotarix® and RotaTeq® and the occurrence of a rare form of bowel obstruction known as intussusception (IS). This is a condition caused by the telescoping of one segment of the bowel into another. It is estimated to occur each year in around 80 per 100 000 children under 12 months of age, which represents approximately 200 cases per year in Australia. The peak incidence is in infants 5–10 months of age, with 80% of cases occurring before 24 months of age. It is much more common in males than females.

IS was found to be a side effect of the first generation rotavirus vaccine, RotaShield®, that was available in the United States in 1998–1999 and was estimated to cause IS in 10–20 of every 100 000 doses given to infants. It was voluntarily withdrawn from the US market in October 1999 (1, 2).

RotaShield® was not used outside the USA, however, as the historical incidence of IS is 2.5 to 3 times higher in infants in Australia than in the US, this would have translated to 25–60 cases of IS for every 100 000 doses of RotaShield®.

Subsequently, two new rotavirus vaccines, Rotarix® and RotaTeq® were developed and both were tested in large studies designed to explore whether there was a risk of IS (3, 4). In Australia, two post-marketing studies have been conducted to investigate whether the new

rotavirus vaccines are associated with an increased risk of IS. The first study was conducted using two surveillance systems, the Paediatric Enhanced Disease Surveillance (PAEDS) and the Australian Paediatric Surveillance Unit (APSU). This study found an apparent four-fold increased risk of IS in babies within one week of being given the first dose of either vaccine, compared with historical data on hospitalizations coded as IS, but no overall increase in overall rates of IS up to the age of nine months.

Following this, a large self-controlled case series (SCCS) study using data on all hospitalized cases coded as IS was commissioned by the TGA. This study found a statistically significant four-fold increase in the occurrence of IS in the first 1–7 days following the first dose of either Rotarix® or RotaTeq® compared with other time periods after vaccine receipt. This increase in risk translates to approximately two additional cases of IS occurring in every 100 000 first doses of vaccine administered, or six additional cases each year in children under 12 months of age in Australia.

The World Health Organization (WHO) and the Australian Technical Advisory Group on Immunization (ATAGI) have recommended the continued use of rotavirus vaccine for infants.

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Tumour necrosis factor blockers: hepatosplenic T-cell lymphoma

United States of America — The Food and Drug Administration (FDA) continues to receive reports of hepatosplenic T-Cell lymphoma (HSTCL), primarily in adolescents and young adults being treated for Crohn disease and ulcerative colitis with medicines known as tumour necrosis factor (TNF) blockers, as well as with azathioprine, and/or mercaptopurine. Crohn disease and ulcerative colitis cause inflammation of the digestive system. Common symptoms are pain in the abdomen, cramps, and diarrhoea. Bleeding from the rectum, weight loss, joint pain, skin problems and fever also may occur. Children with the disease may have growth problems, develop intestinal blockage and experience malnutrition.

FDA believes the risks and benefits of using TNF blockers, azathioprine, and/or mercaptopurine should be carefully weighed when prescribing these drugs to children and young adults, especially for the treatment of Crohn disease and ulcerative colitis.

The product labels for infliximab (Remicade®) and adalimumab (Humira®) have been updated and the product labels for azathioprine and mercaptopurine are being updated to include warnings about HSTCL that have been reported in patients treated with these products.

Reference: *FDA Drug Safety Communication*, 14 April 2011 at <http://www.fda.gov/Drugs/DrugSafety>

Dipeptidyl peptidase-4 inhibitors: possible glycaemic complications

Japan — The Ministry of Health, Labour and Welfare (MHLW) has warned about

the risk of hypoglycaemia associated with concomitant use of dipeptidyl peptidase-4 (DPP-4) inhibitors and sulfonylureas, and the risk of diabetic ketoacidosis and hyperglycaemia after switching from insulin to glucagon-like peptide-1 (GLP-1) receptor agonists.

DPP-4 inhibitors and GLP-1 receptor agonists are antidiabetic drugs which inactivate incretin. Incretin is a gastrointestinal hormone which stimulates insulin secretion. DPP-4 inhibitors are used to treat type 2 diabetes mellitus by increasing the endogenous active incretin level and thereby controlling blood glucose. As of December 2010, sitagliptin phosphate hydrate, vildagliptin, and alogliptin benzoate have been approved in Japan.

GLP-1 receptor agonists are used to treat type 2 diabetes mellitus by binding to the GLP-1 receptor to promote insulin secretion in response to the increase in blood glucose. As of December 2010, liraglutide (genetic recombination) and exenatide have been approved.

Reference: *Pharmaceuticals and Medical Devices Safety Information*, No.275. December 2010 at <http://www.pmda.go.jp/english>

Lenalidomide: risk of new malignancies

United States of America — The Food and Drug Administration (FDA) has provided information on clinical trials that found that patients treated with lenalidomide (Revlimid®) may be at increased risk of developing new types of cancer compared to patients who did not take the drug.

FDA is currently reviewing all available information on this potential risk and recommends that patients continue lenalidomide treatment as prescribed by their physician. The benefits and the risks

should be carefully weighed when prescribing this drug. Lenalidomide is used to treat myelodysplastic syndrome and is used along with other drugs to treat people with multiple myeloma.

Preliminary data derived from evaluation of outcomes after longer-term exposure to lenalidomide and from controlled clinical trials conducted inside and outside the United States shows an increased incidence of some second primary malignancies, particularly acute myelogenous leukemia (AMaL) and B-cell lymphoma malignancies when compared to controls. Since lenalidomide is an analogue of thalidomide, FDA is also currently reviewing all available information on this potential risk for thalidomide.

Reference: *FDA Drug Safety Communication*, 8 April 2011 at <http://www.fda.gov/Drugs/DrugSafety>

Pneumovax 23®: injection site reactions

Australia — The Therapeutic Goods Administration (TGA) is advising health professionals not to administer a second or subsequent dose of Pneumovax 23® vaccine pending the outcome of a review of an apparent increased rate of injection site reactions following administration of the second dose.

Pneumovax 23® vaccination is used to prevent life threatening bacterial infections for anyone who is at high risk of pneumococcal infections.

Pneumovax 23® vaccine is known to be associated with a high rate of local injection site reactions which can include severe injection site reactions such as cellulitis and abscess. There is varying evidence from published trials as to whether injection site reactions are more common following revaccination.

The Australian Technical Advisory Group on Immunization (ATAGI) is currently

reviewing the place of Pneumovax 23® in the National Immunization Programme. This alert is not applicable to use of the 7-valent pneumococcal conjugate vaccine Prevenar® or the 10-valent pneumococcal conjugate vaccine, Synflorix®, which are given to babies.

Reference: Therapeutic Goods Administration Safety Alert. 18 April 2011. <http://www.tga.gov.au/safety/alerts-medicine-pneumovax-110416.htm>

Dabigatran etexilate mesylate capsules: storage and handling

United States of America — The Food and Drug Administration (FDA) is alerting the public to important storage and handling requirements for dabigatran etexilate mesylate (Pradaxa®) capsules. Due to the potential for product breakdown from moisture and loss of potency, Pradaxa® capsules should only be dispensed and stored in the original bottle or blister package. However, many consumers use pill boxes or pill organizers to aid them in remembering to take their medications.

Although the current Pradaxa® label states that the product should be discarded 30 days after the original bottle is opened, data currently under review by the FDA indicate that the product maintains its potency up to 60 days after bottle opening as long as it is stored in the original bottle and the handling requirements are met — including that the cap is closed tightly after use and the bottle is kept away from excessive moisture, heat and cold. Pradaxa® capsules will hydrolyse over time when exposed to humidity, causing a breakdown of active ingredient and rendering the medication less effective.

Reference: *FDA Drug Safety Communication*, 29 March 2011 at <http://www.fda.gov/Drugs/DrugSafety>

Proton pump inhibitors: low magnesium levels

United States of America — The Food and Drug Administration (FDA) is informing the public that prescription proton pump inhibitor (PPI) drugs may cause hypomagnesaemia if taken for prolonged periods of time (in most cases, longer than one year). In approximately one-quarter of the cases reviewed, magnesium supplementation alone did not improve low serum magnesium levels and the PPI had to be discontinued. PPIs are used to treat gastroesophageal reflux disease (GERD), stomach and small intestine ulcers, and inflammation of the esophagus.

Prescription PPIs include esomeprazole magnesium, dexlansoprazole, omeprazole, lansoprazole, pantoprazole sodium, and abeprazole sodium.

Reference: *FDA Drug Safety Communication*, 2 March 2011 at <http://www.fda.gov/Drugs/DrugSafety>

Seasonal influenza vaccines

Australia — During the 2010 influenza season, an excess number of cases of febrile reactions and febrile convulsions were observed in paediatric populations following immunization with one of the registered seasonal trivalent influenza vaccines. Consequently, the Therapeutic Goods Administration (TGA) has imposed a condition on the registration of all 2011 seasonal influenza vaccines with a paediatric indication which were not supplied in Australia in 2010. Sponsors are required to undertake active surveillance of children from six months to nine years of age to ensure effective monitoring of paediatric populations in Australia previously unexposed to these vaccines. Two sponsors were unable to meet this condition of registration. Although the safety of Agrippal® and Fluarix® has been demonstrated in the northern

hemisphere 2010/2011 influenza season, the TGA does not have any safety data on the use of these vaccines in Australian children. Hence, the TGA recommends that these vaccines are not used in any child under the age of nine years.

For children under the age of nine years it is recommended that they be vaccinated with either Influxac® or Vaxigrip®. These two vaccines were not associated with increased rates of fever or febrile reactions in 2010.

Reference: Therapeutic Goods Administration Safety Advisory, 11 March 2011. <http://www.tga.gov.au/safety>

Ipilimumab: severe immune-mediated reactions

United States of America — The Food and Drug Administration (FDA) has posted information from the manufacturer of Ipilimumab (Yervoy®) about the risk evaluation and mitigation strategy (REMS) developed to ensure that the benefits of ipilimumab outweigh the risks of severe and fatal immune-mediated adverse reactions.

Ipilimumab was approved in March 2011 with a boxed warning stating that use of the product can result in severe and fatal immune-mediated adverse reactions due to T-cell activation and proliferation. These immune-mediated reactions may involve any organ system. However, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment. However, a minority occurred weeks to months after discontinuation.

Reference: *FDA Medwatch Communication*, Dear Healthcare Professional Letter, 6 April 2011 at <http://www.fda.gov/Drugs/DrugSafety>

Fluticasone propionate: risk of osteonecrosis

Canada — Health Canada has received five reports of osteonecrosis suspected of being associated with fluticasone propionate.

The potential for osteonecrosis with high doses of inhaled corticosteroids has been suggested in the literature. Because corticosteroid-induced osteonecrosis tends to occur in younger patients and treatment options for advanced disease are limited, early identification is important.

Fluticasone propionate is a highly potent glucocorticoid anti-inflammatory steroid. In Canada, it is available as an aqueous nasal spray, an inhalation aerosol, a powder for inhalation and a topical cream (1–3). Steroid-induced osteonecrosis, or avascular necrosis, is characterized by bone cell death resulting from compromised blood supply. Corticosteroids, administered orally or parenterally, have been associated with osteonecrosis (4). Osteonecrosis related to inhaled or topical use of steroids has also been reported but the oral or parenteral use of steroids was a confounding factor (4). The potential for osteonecrosis with high doses of inhaled corticosteroids, such as in the treatment of severe persistent asthma or eosinophilic oesophagitis, has been suggested (4).

Systemic adverse reactions may occur with intranasal and inhaled use of corticosteroids (1, 2). The long-term effects of fluticasone propionate are still unknown. The relative determinants of systemic adverse reactions to inhaled and intranasal corticosteroids have been assessed and fluticasone propionate was determined to have a high systemic potency (5). Because corticosteroid-induced osteonecrosis tends to occur in younger patients (the average age at onset is 33) and treatment options for advanced

disease are limited, early identification is important (4).

Extracted from the Canadian Adverse Reaction Newsletter, Volume 21(2), April 2011 at <http://www.healthcanada.gc.ca>

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Varenicline: hyperglycaemia in patients with diabetes

Canada — Health Canada has received 18 reports of hyperglycaemia suspected of being associated with varenicline (Champix®) in patients with type 1 and type 2 diabetes.

Varenicline is indicated for smoking-cessation treatment in adults in conjunction with smoking-cessation counselling. The current Canadian product monograph lists diabetes mellitus and hypoglycaemia under “less common clinical trial adverse drug reactions” and describes these adverse reactions (ARs) as infrequent and rare, respectively.

Diabetes mellitus is a chronic metabolic disorder characterized by the presence of hyperglycaemia and consequently is a

confounder. Other confounders identified in some of the reports included infection, medications (e.g., insulin, oral antidiabetic agents, diuretics), alcohol consumption and smoking cessation. In some instances, the patient was still smoking while taking varenicline.

Extracted from the Canadian Adverse Reaction Newsletter, Volume 21(2), April 2011 at <http://www.healthcanada.gc.ca>

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Quinine sulfate: serious adverse reactions

Canada — Quinine sulfate, in combination with a second antimalarial drug, is recommended for the treatment of uncomplicated *Plasmodium falciparum* malaria. Quinine sulfate is not indicated in Canada for the prevention or treatment of nocturnal leg cramps. However, quinine sulfate is used for the prevention and treatment of leg cramps, at a dose of 200 to 300 mg at bedtime. The use of quinine sulfate to prevent leg cramps has been a subject of recent concern. Several international regulators have taken action to either withdraw this indication for use or have added conditions for its use for leg cramps.

Adverse reactions to quinine sulfate include life-threatening blood-related reactions, such as sudden, severe thrombocytopenia.

Extracted from the Canadian Adverse Reaction Newsletter, Volume 21(2), April 2011 at <http://www.healthcanada.gc.ca>

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Risk of oral clefts in children born to mothers taking topiramate

United States of America — The Food and Drug Administration (FDA) is informing the public of new data that show that there is an increased risk for the develop-

ment of oral clefts in infants of women treated with topiramate (Topamax® and generic products) during pregnancy.

Topiramate is an anticonvulsant used to treat epilepsy. It is approved for use to prevent migraine headaches. Topiramate is being placed in Pregnancy Category D indicating positive evidence of human fetal risk but with potential benefits that may be acceptable in certain situations despite its risks.

Reference: *FDA Drug Safety Communication*, 4 March 2011 at <http://www.fda.gov/Drugs/DrugSafety>

WHO training course on pharmacovigilance

A recent survey by the WHO Programme for International Drug Monitoring identified serious gaps in technical capacity for pharmacovigilance (PV) in resource limited settings. The Inter-regional Pharmacovigilance Training Course, held in February 2011 in New Delhi, India, was part of the WHO strategy to help establish minimum standards for PV as identified by WHO and the Global Fund during a consensus meeting in 2010.

The course identified leveraging opportunities offered by liaison and sharing resources with lymphatic filariasis public health programmes. By introducing PV within mass preventive treatment campaigns, the quality of care and patient safety within such programmes could be significantly improved.

The specific objectives of the training course were to:

- Raise awareness about public health issues and patient safety in relation to the use of medicines.
- Demonstrate the importance of PV activities in improving patient safety and treatment outcomes.

- Provide training on the latest tools in basic adverse drug reaction (ADR) reporting, to enhance reporting within countries and to the WHO Programme for International Drug Monitoring.
- Build or reinforce capacity of national PV centres.
- Share experiences and challenges faced in establishing or strengthening PV programmes.
- Establish networking among regulatory agencies, PV centres, national neglected tropical diseases (NTD) control programmes and WHO for information sharing and providing assistance in detecting signals and making judgments based on sound science.

Two participants per country attended from Cambodia, Lao PDR, Maldives, Nepal and Viet Nam, with six participants from India. Others represented the national PV centre or the NTD control programme.

The five-day course covered the following topics:

- WHO Programme for International Drug Monitoring.
- Establishing a PV centre; how to promote reporting.
- Vigibase (a WHO global database of individual case reports), VigiFlow (a web-based case report management system), WHO Adverse Reaction Terminology and WHO Drug Dictionary.
- Causality assessment.
- Collaboration with public health programmes and NTD control programmes in particular.
- Risk management and the prevention of ADRs.

- Rational use of medicines.
- Communication in pharmacovigilance.
- Development of country-specific action plans for next year.

At the end of the course participants presented draft plans of priority activities for the next ten months for PV in their settings, with key deliverables, timelines and expected outcomes.

Countries that are not yet members of the WHO Programme (Lao PDR, Maldives) described their plans to establish a PV centre and join the Programme in the future. Participants from Cambodia, an associate member of the WHO Pro-

gramme, expressed their intention to become a full member by sending a required number of ADR reports to the WHO Programme. Three countries that are members of the WHO Programme — India, Nepal, and Viet Nam — presented plans to strengthen or expand their current PV work by holding workshops on PV for stakeholders, improving collaboration between PV and public health programmes and other actions. Participants from Nepal and Viet Nam confirmed that the course was useful in establishing collaboration for the first time between the national PV and the NTD control programmes.

Reference: World Health Organization. *Pharmaceutical Newsletter*, April 2011 at <http://www.who.int/medicines>

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.

Quality Assurance Issues

WHO Certification Scheme

The WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce is an international voluntary agreement mechanism which provides information to participating countries on the quality status of finished pharmaceutical products moving in international commerce. The primary focus of the Scheme is the Certificate of a Pharmaceutical Product (CPP).

The WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSP) recommended that the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce should be reviewed in line with changing practices and rapid globalization of the pharmaceutical manufacturing sector, regulatory environment and procurement systems. However, the Scheme can only be opened for revision by decision of the World Health Assembly (1). As an interim measure, the ECSP requested that a question and answer document on the functions of the Scheme should be prepared (2). Version one of the document has been developed with the aim of improving understanding of the objectives of the Scheme and its implications for quality improvement and provision of effective, safe medicines by participating countries. Comments and suggestions on this document may be sent to Dr Samvel Azatyan, Medicines Regulatory Support Programme, World Health Organization, 1211 Geneva 27, Switzerland, or e-mail: azatyan@who.int.

WHO Certification Scheme: questions and answers

Q1 What is the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce?

A1 It is a Scheme developed by the World Health Organization (WHO) in response to the request of WHO Member States to facilitate international trade in pharmaceutical products between Member States.

Q2 When was the Scheme developed?

A2 It was first developed in 1975. Since then it has been revised in 1988, 1992 and in 1997.

Q3 How can it facilitate trade in pharmaceutical products?

A3 The Scheme is an administrative instrument that requires a participating Member State (a certifying country), upon application by a commercially interested party (the applicant company), to certify/attest to the competent authority of another participating Member State (the recipient country) that:

- A specific pharmaceutical product is authorized for marketing in the certifying country, or if not, the reason why authorization has not been accorded.
- The manufacturing facilities and operations conform to good manufacturing practices (GMP) as recommended by WHO.

Q4 Why is it called the WHO Certification Scheme?

A4 It is called the WHO Certification Scheme because it was developed by WHO in response to the request of Member States.

Q5 How does the Scheme operate?

A5 The Scheme operates as follows: The certificate recipient authority has in its national medicine legislation or guidelines a requirement for the submission of a Certificate for a Pharmaceutical Product (CPP) for products being imported into the country as a support to ensure the quality of the product being imported. (In some countries the CPP forms part of the dossiers to be submitted to the medicines regulatory authority (MRA) to have a product registered by the authority).

The applicant/importing company requests a CPP from the certifying authority through the exporting company.

The certifying authority issues a CPP to the importing/applicant company via the exporting company. At the time of the development of the Scheme the understanding was that a CPP would be sent directly to the recipient authority by the issuing authority.

Q6 Is the Scheme mandatory?

A6 No. The Scheme is not mandatory. It is a voluntary agreement devised to enable countries with limited regulatory capacity to obtain partial assurance from exporting countries concerning the quality, safety and efficacy of the pharmaceutical product they plan to import.

Q7 Can anyone issue a CPP?

A7 No. Only countries and regional organizations such as the European Medicines Agency (EMA) that are party to the Scheme can issue a CPP.

Q8 How can a WHO Member State or regional organization be eligible for participation in the Scheme?

A8 Any WHO Member State or regional organization intending to participate in the Scheme may do so by notifying the Director-General of WHO in writing:

- Of its willingness to participate in the Scheme.
- Of any significant reservations it intends to observe relating to its participation.
- By providing the names and address of its MRA or other competent authority.

Q9 Where can one find the list of organizations and countries party to the Scheme?

A9 WHO publishes the names and addresses of Member States party to the Scheme. The list is available at http://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/en/index.html. A hard copy of the list is also published and distributed to Member States. The list is regularly updated.

Q10 Does the list of Member States and organizations party to the Scheme provide the names and addresses of those government organizations authorized to sign and issue a CPP?

A10 Yes. The list provides the names and full addresses of those government organizations authorized to sign and issue a CPP. MRAs receiving a CPP can use this list to check and verify if the certificate they are receiving has been issued by the authorized organization.

Q11 Is there any written document that provides detailed information on the WHO Certification Scheme?

A11 Yes. Guidelines for implementation of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce are available at http://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/guidelines/en/index.html" http://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/guidelines/en/index.html.

Q12 What should Member States and regional organizations possess in order to issue a CPP to support the export pharmaceutical products?

A12 In order to issue a CPP, Member States and regional organizations should have the following infrastructure and systems in place:

- An effective national licensing system for pharmaceutical products, manufacturers and distributors.
- GMP requirements consonant with those recommended by WHO to which all manufacturers of finished pharmaceutical products (FPPs) are required to conform.
- Effective controls to monitor the quality of pharmaceutical products registered or manufactured within the country, including access to an independent quality control laboratory.
- A national pharmaceutical inspectorate having the technical competence, experience and resources to assess whether GMP and other controls are effectively implemented and the legal power to conduct appropriate investigations.
- The administrative capacity to issue the required certificates, to institute inquiries in the case of a complaint associated with a potentially serious quality defect or other hazard and to notify WHO and other concerned parties.

Q13 Does WHO issue CPPs?

A13 No. WHO does not issue CPPs or any of the certificates described under the Scheme.

Q14 Should a CPP issued by Member States bear the WHO emblem or refer to the WHO acronym?

A14 No. Certificates should not bear the WHO emblem or the acronym. Use of the emblem or acronym creates the impression that the certificate is issued or endorsed by WHO. This is an illegal act and countries receiving such CPPs should reject them and report such practices to WHO.

Q15 What products are covered under the WHO Certification Scheme?

A15 Pharmaceutical products are covered under the Scheme and include:

- FPPs intended for administration to human beings.
- Pharmaceutical products intended for administration to food-producing animals.
- Active pharmaceutical ingredients (APIs). There is now a separate scheme called the WHO pharmaceutical starting materials certification scheme (SMACS) which has guidelines on importation of APIs.

Q16 What are the different types of Certificate that can be requested within the scope of the Scheme?

A16 Three types of certificate can be requested within the scope of the Scheme:

- A Certificate for a Pharmaceutical Product (CPP) or Product Certificate (PC);

- A Statement of Licensing Status of Pharmaceutical Product(s) (SLSP);
- Batch Certificate of a Pharmaceutical Product (BCPP).

Q17 By whom and when is a Certificate for a Pharmaceutical Product (CPP) issued?

A17 A CPP is issued by the competent authority of the exporting country and is intended for use by the competent authority of the importing country:

- When a pharmaceutical product is under consideration for a product licence/marketing authorization for importation and sale in the importing country.
- When administrative action is required to renew, extend, vary or review such licence.

Q18 When and by whom is a Statement of Licensing Status of Pharmaceutical Product(s) (SLSP) issued?

A18 An SLSP is issued by the competent authority of the exporting country and is intended for use by importing agents when considering bids in an international tender. It is requested by the importing agent as a condition for bidding.

Q19 What is a Batch Certificate?

A19 A Batch Certificate accompanies and attests to the quality and expiry date of a specific batch or consignment that has already been licensed/approved for marketing in the importing country.

A batch certificate is usually issued by the manufacturer.

In case of biological products, a lot certificate is issued by the competent authority of the exporting country.

Q20 Is there a standard format for CPPs?

A20 Yes, there is a standard format. The WHO standard format was last agreed by the World Health Assembly in 1997 (1).

The standard WHO format for CPPs facilitates understanding and review by the recipient authority. It obliges certifying authorities to disclose important information to the importing country.

Recipient authorities should refrain from obtaining data other than in the WHO standard format or in addition to the standard CPP format.

Certifying authorities should not issue a free-sale certificate. This has been replaced by the WHO format CPP.

Q21 Is the CPP evidence of quality, safety, efficacy review and approval?

A21 Yes, the CPP is based on the assumption that the authorities issuing a CPP have the capacity to assess the quality, safety, and efficacy (QSE) of the product they have approved for marketing.

Based on the intention of the Scheme and when evidence of approval in another country is required, a recipient authority may request a CPP if it is unable to undertake a full review of QSE data.

Q22 Does the CPP provide evidence of good manufacturing practices (GMP) status?

A22 Yes. The GMP declaration in the CPP refers to assurance of GMP for the product approved in the certifying country at the stated manufacturing site.

In addition, certificates from medicines regulatory authorities (MRAs) party to the Pharmaceutical Inspection Cooperation

Scheme (PIC/S) and International Conference on Harmonisation (ICH) (USA, Japan, and EU) provide evidence of GMP status.

Q23 What is the difference between approval of the quality data in the submission and evidence of GMP?

A23 Approval of the quality information in a submission is a determination of how the applicant proposes to manufacture and control the quality of the product at the time of manufacture and throughout the life of the product.

Evidence of GMP compliance confirms that the applicant company has been able to demonstrate that the manufacturing facilities and operations conform to good manufacturing practices (GMP) as recommended by WHO.

Q24 When would a CPP be required?

A24 When the CPP replaces either a full or partial quality, safety and efficacy (QSE) review. The CPP would be a condition of approval but it would not be required at the time of submission.

If local legislation stipulates provision of a CPP at the time of submission, the authority review should comprise a verification procedure with published, communicated timelines that should be short and avoid delaying patient access.

Q25 Are there any alternatives to a CPP as evidence of approval by an MRA?

A25 In addition to the WHO Certification Scheme other forms of evidence include:

- Product approval letters (or copies of licences) from well-established MRAs, e.g., Australia, Canada, China, Denmark, Finland, Germany, India, Japan, Norway, Republic of Korea, Spain, United Kingdom, United States of America.

- Positive scientific opinion from the European Medicines Agency (EMA).
- Decisions of the European Commission.
- Licensing/approval information on regulatory authority web sites.
- Evidence of approval on the United States Food and Drug Administration web site.

Q26 Is it necessary for a pharmaceutical product to be exported from the same country as the certifying authority?

A26 No. It is not necessary for the product to be exported from the certifying country as long as a declaration of GMP assurance appears on the CPP.

The Scheme was established on the basis that the certifying country was also the country where finished product manufacture took place and was, therefore, the exporting country. Subsequent revisions to the Scheme allow scope for CPPs to be issued by other reference authorities. Most certifying authorities currently provide CPPs when the finished product is not manufactured in the certifying country on the basis of GMP assurance.

Many authorities assume that certifying authorities issue CPPs even when finished product manufacture does not occur in the certifying country. Strict adherence to the above assumption potentially limits licensing and registration options and can delay the introduction or affect the continued supply of needed medicines.

Q27 Is it possible to obtain a CPP from a certifying authority that is not of the country where the manufacture of the finished product takes place?

A27 Yes. The GMP declaration on the CPP will refer to assurance of GMP for

the product approved in the certifying country at the stated site, even if the manufacturing site is in a different country than the issuing authority.

The Scheme has a provision that when manufacture takes place in a country other than that where the product certificate is issued, an attestation that such manufacture complies with GMP may still be provided as an attachment to the product certificate on the basis of inspections undertaken for registration purposes.

Q28 Is it necessary for the CPP to come from the country where finished product manufacture takes place?

A28 No. Although the Scheme was set up assuming that the certifying country was also the country where finished product manufacture takes place, there is scope within the Scheme for CPPs to be issued by other authorities that can provide independent assurance of the GMP compliance status.

There needs to be an appreciation of the complexity of manufacturing and sourcing routes currently employed by companies operating internationally. WHO Member States may define the source differently:

- Country of finished product manufacture.
- Country of final packing.
- Country of final release.
- Country of headquarters of the pharmaceutical company, etc.

A critical element is confirmation that all production/manufacturing/quality operations are carried out according to GMP.

Due to complex modern sourcing routes, together with varying local regulatory

processes, approval in the country where finished product manufacture takes place may be subsequent to that in other countries. In this case it is a matter of judgment whether it is necessary for the CPP to be issued from the country where finished product manufacture takes place. Preferred action, in order to speed up patient access, would be to accept the CPP from the earlier approving country. In order to approve the product the certifying authority must be assured of GMP.

GMP implementation and compliance ensures product quality. Any requirement for an additional CPP for the release site, if it is different from the product manufacture site, will delay patient access because multiple CPPs provide no additional value.

Q29 What is the significance of the declaration of marketing status (i.e., whether the product is actually on the market in the exporting country)?

A29 A declaration of marketing authorization approval is the aim of the CPP. It is true that the WHO format CPP includes information on marketing status (if the product is actually on the market of the exporting country) but the Scheme also has a provision whereby the issuing authority can indicate why the product may not be marketed. In circumstances where the product is not actually on the market, the issuing authority can indicate this on the certificate.

The actual presence on the market of the product depends on many other factors. The recipient authority should not require that a product be marketed in the certifying country.

Q30 Should recipient authorities require a CPP from more than one certifying authority?

A30 No. They should not require a CPP from more than one certifying authority. A WHO-format CPP from a single certifying authority should provide appropriate evidence of approval and GMP status.

Q31 Is it necessary for recipient authorities to require GMP certificates in addition to a CPP?

A31 No. Since the CPP includes a GMP declaration, additional GMP certificates are not necessary.

Following introduction of the WHO CPP some authorities no longer issue GMP certificates (e.g., US FDA).

In the presence of a CPP, separate GMP certificates are redundant and are therefore discouraged. CPPs should be accepted (in particular from PIC/S and ICH countries) as evidence of GMP status.

However, outside of the Scheme, there are occasions when it is appropriate to require a GMP certificate.

Q32 When a CPP forms part of a regulatory review, is it necessary to conduct a site inspection as well?

A32 An inspection should not be necessary when the GMP declaration on the CPP covers the product to be approved in the recipient country.

Inspections outside of this condition are a decision which should be made by the recipient country. Mechanisms and systems for recognizing inspections carried out by other authorities is encouraged to reduce duplication of inspections.

CPPs should be accepted (in particular from PIC/S and ICH countries) as evidence of GMP status. The decision to inspect should be made after a risk-based assessment of the facility, taking into account GMP and inspection status provided by other authorities.

Q33 Imagine a situation in which company A in one European country called M produces a pharmaceutical product called X and the product is authorized for marketing in that country. Company A also produces X under contract manufacturing in country Z in Asia and wants to export it to country Y in Africa. The authority in the importing country Y requires a CPP to approve importation. (See figure 1 overleaf.)

The questions are:

Q33a Is contract manufacturing accepted?

A33a Yes. Contract manufacturing is accepted under GMP.

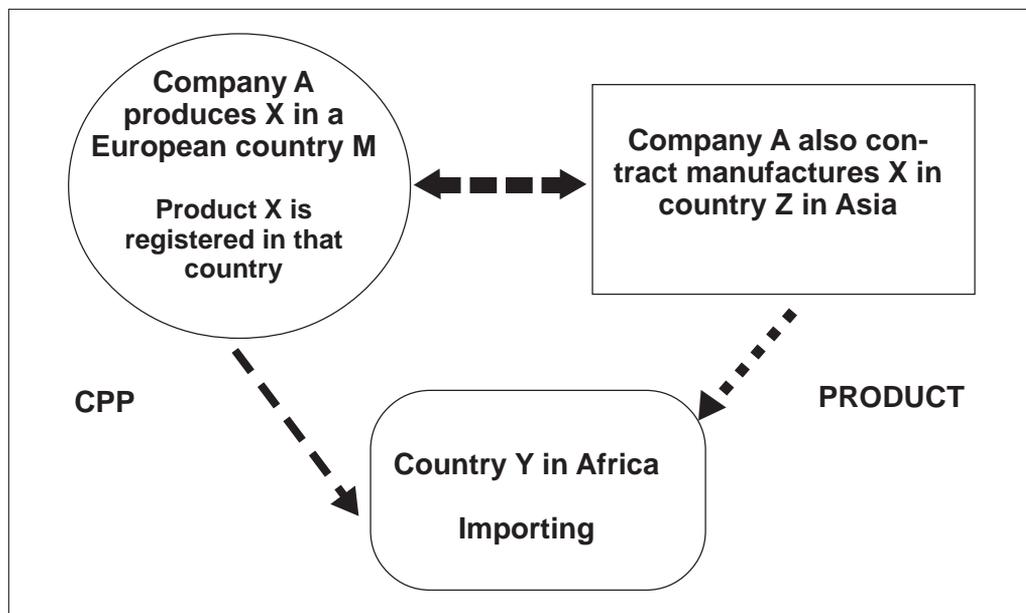
Q33b In the case of a contract-manufactured product, from which country should the authority in the importing country (receiving authority) accept the CPP?

A33b Country Z can issue a CPP if the product is registered by the authority of country Z. If the product is not registered in Z then the authority in Z cannot issue the CPP.

If the contract-manufactured product is also authorized for marketing in the European country, then the European country can issue the certificate.

If the product is not registered in both countries, then the only country that can issue a certificate will be the European country, M. The authority of the European country will issue the CPP after it has satisfied itself that the product under contract manufacture is the same in all aspects as the one produced in its own country and that the product is produced in compliance with GMP.

Q34 Can a CPP also be used to provide evidence of an administrative review and approval, e.g., as certification of acceptability of a company name change?

Figure 1. Question 33: contract manufacturing

A34 Yes. The CPP can also provide evidence of an administrative review and approval (e.g., as certification of acceptability of a company name change, or for a name change of the owner of a manufacturing or production site) which often happens in the context of company mergers and acquisitions.

For administrative approvals that now involve a QSE review, recipient authorities should use alternatives to a CPP as a preferred and quicker option (see Question 9).

Issues related to manufacturing company name change (administrative review) may indeed create various practical difficulties for exporters–importers but are not associated directly with safety/quality concerns and should be given less prominence.

Q35 Imagine a situation in which a product is authorized for marketing in the country of manufacture but is not actually available on the market. Can the compe-

tent authority of the exporting country issue a CPP to support export?

A35 Yes, it can issue a CPP. What it should do is explain why it is not on the market. One reason for not being on the market could be that the disease/health problem for which the product is indicated may not be prevalent in the country.

Q36 Sometimes a country may wish to import a special dosage form, strength or formulation of a certain known product and this particular product may not be registered in the manufacturing country. Under such circumstances can the authority of the exporting country issue a CPP?

A36 Yes. It can issue a CPP but it should explain on the certificate that the particular product is not authorized for marketing in the exporting country, that it has been produced based on the request of the importing country and that manufacturing is in compliance with GMP.

Q37 Is it necessary to legalize the CPP?

A37 No. Legalization is not part of the WHO Scheme and it is not considered to provide additional assurance of authenticity. Approval status in key reference countries is currently available as public information.

Legalization should not be necessary since an official governmental authority of the certifying country signs the CPP. Legalization delays availability of the CPP and thereby delays access to medicines for patients. If a recipient authority has any doubts about the validity of a CPP it should contact the certifying authority directly.

Q38 What should receiving countries do in case of any doubt about a CPP?

A38 In case of any doubt, the competent authorities of receiving countries should communicate directly with the authorized body that has issued the certificate or contact WHO to clarify the matter.

Q39 Are certifying authorities penalized if they issue CPPs, but do not meet WHO requirements for self-certification and subsequent issue of CPPs?

A39 No. There is no penal system. WHO does not have the power to certify, inspect or penalize certifying authorities.

Q40 What are the main problems encountered in the application of the Scheme?

A40 A number of problems have been reported during use of the Scheme, which include:

- Countries not party to the Scheme issue certificates.
- Authorities that do not meet the requirements stated in the guidelines for the Scheme issue certificates.
- Some issuing authorities put the WHO emblem, logo or acronym on the certificate, thereby creating the impression that the certificate is authenticated by WHO.

References

1. WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. World Health Assembly resolution WHA22.50 (1969), World Health Assembly resolution WHA28.65 (1975), World Health Assembly resolution WHA41.18 (1988), World Health Assembly resolution WHA45.29 (1992), and World Health Assembly resolution WHA50.3 (1997) available at: <http://www.who.int/governance>
2. World Health Organization. Expert Committee on Specifications for Pharmaceutical Preparations. *Technical Report Series*, 2009;953:47-48 at <http://www.who.int/medicines/publications>.

Regulatory Action and News

Buflomedil: marketing authorization suspended

France — On 11 February 2011, the Health Products Safety Agency (AFSSPS) suspended the marketing authorization for buflomedil-containing products. This action was taken following notification of serious nervous and cardiac events especially during accidental or voluntary overdose.

Reference: Spécialités à base de Buflométil – Retrait de produits. 17 February 2011 at <http://www.afssaps.fr>

Dolasetron mesylate intravenous injection: withdrawal

Canada — The manufacturer of dolasetron mesylate (Anzemet®) has announced withdrawal of the injectable form. New data show that intravenous administration of the injectable form of dolasetron mesylate is associated with QTc prolongation to an extent which may potentially result in serious arrhythmias at the doses recommended for the prevention of nausea and vomiting associated with chemotherapy. Dolasetron mesylate injectable is no longer indicated to prevent nausea and vomiting in adults undergoing chemotherapy.

However, tablets for oral use may still be used as the risk of developing an abnormal heart rhythm with the oral form of this drug is considered less than that seen with the injectable form.

Reference: Health Canada, Medeffect. 26 April 2011. <http://www.healthcanada.gc.ca/medeffect> and <http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/new-neuf-advisories-avis-eng.php>

Abiraterone acetate approved for late-stage prostate cancer

United States of America — The Food and Drug Administration (FDA) has approved abiraterone acetate (Zytiga®) in combination with prednisone to treat patients with metastatic castration-resistant prostate cancer who have received prior docetaxel.

Patients who received the Zytiga® and prednisone combination had a median overall survival of 14.8 months compared to 10.9 months for patients receiving the placebo and prednisone combination.

The most commonly reported side effects included joint swelling or discomfort, low levels of potassium in the blood, fluid retention (usually of the legs and feet), muscle discomfort, hot flashes, diarrhoea, urinary tract infection, cough, high blood pressure, heartbeat disorders, urinary frequency, increased night-time urination, upset stomach or indigestion and upper respiratory tract infection.

Reference: *FDA News Release*, 28 April 2011 at <http://www.fda.gov>

Rituximab approved for Wegener granulomatosis and microscopic polyangiitis

United States of America — The Food and Drug Administration (FDA) has approved rituximab (Rituxan®) in combination with glucocorticoids to treat patients with Wegener granulomatosis (WG) and microscopic polyangiitis (MPA), two rare disorders that cause vasculitis.

Rituximab is an antibody that is manufactured through biotechnology methods.

Safety and effectiveness was demonstrated in a single controlled trial in which 197 patients with WG or MPA were assigned at random to receive either Rituxan® plus glucocorticoids once a week for four weeks or oral cyclophosphamide plus glucocorticoids daily to induce remission. After six months, 64% of patients treated with Rituxan® had complete remission compared to 53% of patients treated with cyclophosphamide.

Rituximab carries a boxed warning for infusion reactions. Other boxed warnings include severe mucocutaneous reactions and progressive multifocal leukoencephalopathy. Rituximab is not recommended for use in patients with severe, active infections.

The most common side effects in study participants with WG and MPA included infection, nausea, diarrhoea, headache, muscle spasms, and anaemia.

Rituximab, which has been marketed since 1997, is also indicated for the treatment of patients with non-Hodgkin lymphoma, chronic lymphocytic leukaemia, and rheumatoid arthritis.

Reference: *FDA News Release*, 19 April 2011 at <http://www.fda.gov>

Human normal immunoglobulin: lifting of suspension

European Union — The European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) has recommended the lifting of the suspension of the marketing authorizations for human normal immunoglobulin 5% and 10% (Octagam®) and associated names, and the re-introduction of the medicine onto the market in the European Union.

The lifting of the suspension is subject to a change in the manufacturing process. Human normal immunoglobulin is an

intravenous solution used to strengthen the body's immune system.

The CHMP recommended the suspension of the marketing authorizations following an unexpected increase in reports of thromboembolic reactions, including stroke, myocardial infarction and pulmonary embolism in patients receiving the medicine.

An in-depth review of all available data on the safety and quality issues identified previously has now been finalized. The CHMP has concluded that the unexpected presence of a pro-coagulant, factor XIa, was the main cause of the thromboembolic events and that a number of critical steps in the manufacturing process could explain the presence of substances that triggered the thromboembolic events.

The Committee's opinion has now been forwarded to the European Commission for the adoption of a legally binding decision. It is expected that supply of Octagam® will resume shortly after the adoption of the Commission decision.

Reference: *EMA Press Release*, EMA/297816/2011, 14 April 2011 at <http://www.ema.eu>

Everolimus approved for pancreatic cancer

United States of America — The Food and Drug Administration (FDA) has approved everolimus (Afinitor®) to treat patients with progressive neuro-endocrine tumours located in the pancreas (PNET) that cannot be removed by surgery or have become metastatic.

Neuro-endocrine tumours found in the pancreas are slow-growing and rare. It is estimated that there are fewer than 1000 new cases in the United States each year.

The most commonly reported side effects included stomatitis, rash, diarrhoea, fatigue, edema, abdominal pain, nausea, fever and headache.

Afinitor® is also approved to treat patients with advanced renal cell carcinoma after they fail treatment with sunitinib or sorafenib, and patients with subependymal giant cell astrocytoma associated with tuberous sclerosis who cannot be treated with surgery.

Reference: *FDA News Release*, 6 May 2011 at <http://www.fda.gov>

Boceprevir approved for hepatitis C

United States of America — The Food and Drug Administration (FDA) has approved boceprevir (Victrelis®) to treat certain adults with chronic hepatitis C. Boceprevir is used for patients who still have some liver function and who either have not been previously treated with drug therapy for hepatitis C or who have failed such treatment. Boceprevir is approved for use in combination with peginterferon alfa and ribavirin.

Safety and effectiveness of boceprevir was evaluated in two phase III clinical trials with 1500 adult patients. In both trials, two-thirds of patients receiving boceprevir in combination with pegylated interferon and ribavirin experienced a significantly increased sustained virologic response.

According to the US Centers for Disease Control and Prevention, about 3.2 million people in the United States have chronic hepatitis C. Most liver transplants performed in the United States are due to progressive liver disease caused by hepatitis C virus infection.

Reference: *FDA News Release*, 13 May 2011 at <http://www.fda.gov>

Linagliptin approved for type 2 diabetes

United States of America — The Food and Drug Administration (FDA) has approved linagliptin (Tradjenta®) tablets for use with diet and exercise, to improve blood glucose control in adults with Type 2 diabetes which is the most common form of the disease, affecting between 90 and 95% of the 24 million diabetics in the United States.

Linagliptin was demonstrated to be safe and effective in eight double-blind, placebo-controlled clinical studies involving about 3800 patients with Type 2 diabetes.

Linagliptin has been studied as a stand-alone therapy and in combination with other type 2 diabetes therapies including metformin, glimepiride, and pioglitazone. Linagliptin has not been studied in combination with insulin, and should not be used to treat people with type 1 diabetes or in those who have diabetic ketoacidosis.

Reference: *FDA News Release*, 2 May 2011 at <http://www.fda.gov>

Naproxcinod: withdrawal of marketing authorization application

European Union — The European Medicines Agency (EMA) has been notified by the manufacturer of its decision to withdraw its application for a centralized marketing authorization for the medicine naproxcinod (Beprana®), 375 mg hard capsules.

Naproxcinod was intended to be used for the relief of the signs and symptoms of osteoarthritis of the knee and hip in adults.

In its official letter, the company stated that their decision to withdraw the appli-

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

Reference: *EMA Press Release, EMA/322628/2011*, 20 April 2011 at <http://www.ema.eu>

Lumiracoxib: withdrawal of marketing authorization application

European Union — The European Medicines Agency (EMA) has been notified by the manufacturer of its decision to withdraw its application for a centralized marketing authorization for the medicine lumiracoxib (Jocicela®) 100 mg film-coated tablets. Lumiracoxib was intended to be used for symptomatic relief in the treatment of osteoarthritis of the knee and hip in patients who are non-carriers of the DQA1*0102 allele.

In its official letter, the company stated that its decision to withdraw the application was based on its inability to address the CHMP request to provide additional data within the timeframe allowed in the centralized procedure.

Reference: *EMA Press Release, EMA/309990/2011*, 18 April 2011 at <http://www.ema.eu>

Erythropoietin: withdrawal of marketing authorization application

European Union — The European Medicines Agency (EMA) has been notified by the manufacturer of its deci-

sion to withdraw its application for a centralized marketing authorization for the medicine erythropoietin (Epostim®), 2000 IU/ 0.5 ml, 4000 IU/0.4 ml, and 10 000IU/ml solution for injection in pre-filled syringes.

This medicine was intended to be used for the following indications:

- Treatment of anaemia associated with chronic renal failure in paediatric and adult patients on haemodialysis and adult patients on peritoneal dialysis.
- Treatment of severe anaemia of renal origin accompanied by clinical symptoms in adult patients with renal insufficiency not yet undergoing dialysis.
- Treatment of anaemia and reduction of transfusion requirements in adult patients receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma.
- To increase the yield of autologous blood from patients in a predonation programme.
- To reduce exposure to allogenic blood transfusions in adult non-iron deficient patients prior to major elective orthopaedic surgery.

In its official letter, the company stated that its decision to withdraw the application was based on its inability to address the CHMP's request to provide additional data within the timeframe allowed in the centralized procedure.

Reference: *EMA Press Release, EMA/271900/2011*, 6 April 2011 at <http://www.ema.eu>

ATC/DDD Classification

ATC/DDD Classification (temporary)

The following anatomical therapeutic chemical (ATC) classifications and defined daily doses (DDDs) were agreed by the WHO International Working Group for Drug Statistics Methodology March 2011. Comments or objections to the decisions should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology at whocc@fhi.no. The new ATC codes and DDDs will be considered final and be included in the January 2012 issue of the ATC index. The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy. The WHO Collaborating Centre for Drug Statistics Methodology can be contacted through e-mail at: whocc@fhi.no.

ATC level	INN/Common name	ATC code
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New ATC 5th level codes:

abiraterone	L02BX03
aflibercept	S01LA05
axitinib	L01XE17
bosutinib	L01XE14
brentuximab vedotin	L01XC12
catridecacog	B02BD11
crizotinib	L01XE16
dapagliflozin	A10BX09
dexlansoprazole	A02BC06
levomethadone	N07BC05
losartan and amlodipine	C09DB06
meloxicam, combinations	M01AC56
mipomersen	C10AX11
naproxen and misoprostol	M01AE56
pasireotide	H01CB05
perampanel	N03AX22
ruxolitinib	L01XE18
sipuleucel-T	L03AX17
tafamidis	N07XX08
telaprevir	J05AE11
tesamorelin	H01AC06
vemurafenib	L01XE15

ATC name changes

Previous	New	ATC code
Antigrowth hormones	Somatostatin and analogues	H01CB
Calcium, combinations with other drugs	Calcium, combinations with vitamin D and/or other drugs	A12AX
Enzyme inhibitors	Aromatase inhibitors	L02BG

New DDDs:

INN/common name	DDD	Unit	Adm.R	ATC code
aspoxicillin	4	g	P	J01CA19
aztreonam	0.225	g	Inhal. solution	J01DF01
bekanamycin	0.6	g	P	J01GB13
carumonam	2	g	P	J01DF02
cefbuperazone	2	g	P	J01DC13
cefminox	4	g	P	J01DC12
conestat alfa	3.5	TU	P	B06AC04
desvenlafaxine	50	mg	O	N06AX23
fingolimod	0.5	mg	O	L04AA27
flomoxef	2	g	P	J01DC14
histrelin	0.137	mg ¹	implant	H01CA03
isepamicin	0.4	g	P	J01GB11
ribostamycin	1	g	P	J01GB10
tapentadol	0.4	g	O	N02AX06
ticagrelor	0.18	g	O	B01AC24
vernakalant	0.2	g	P	C01BG11

¹. DDD assigned according to the total content of the implant.

Herbal medicinal products***New ATC 5th level codes::**

Name	ATC code
St. John's Wort	N06AX25

². Assessed and approved by regulatory authorities based on dossiers including efficacy, safety, and quality data (e.g., well-established use procedure in EU).

.../...

ATC/DDD Classification

ATC/DDD Classification (final)

The following anatomical therapeutic chemical (ATC) classifications and defined daily doses (DDDs) were agreed by the WHO International Working Group for Drug Statistics Methodology in October 2010. They will be included in the January 2012 issue of the ATC index. The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy. The WHO Collaborating Centre for Drug Statistics Methodology can be contacted at whocc@fhi.no.

ATC level	INN/Common name	ATC code
New ATC level codes (other than 5th level):		
	Drugs used in hereditary angioedema	B06AC
New ATC 5th level codes:		
	aspoxicillin	J01CA19
	azilsartan medoxomil	C09CA09
	bekanamycin	J01GB13
	cabazitaxel	L01CD04
	carumonam	J01DF02
	cefbuperazone	J01DC13
	cefminox	J01DC12
	cinchocaine	S02DA04
	conestat alfa	B06AC04
	dienogest	G03DB08
	dimeticone	P03AX05
	donepezil and memantine	N06DA52
	doxylamine, combinations	R06AA59
	ecallantide	B06AC03
	emtricitabine, tenofovir	
	disoproxil and rilpivirine	J05AR08
	flomoxef	J01DC14
	fluidione	B01AA12
	iloperidone	N05AX14
	ipilimumab	L01XC11
	meningococcus B, multi-component vaccine	J07AH09
	metformin and linagliptin	A10BD11
	metformin and saxagliptin	A10BD10
	motavizumab	J06BB17
	panobinostat	L01XX42
	pentosan polysulfate sodium	G04BX15

.../...

ATC level	INN/Common name	ATC code
	pirfenidone	L04AX05
	ramipril and amlodipine	C09BB07
	rilpivirine	J05AG05
	secukinumab	L04AC10
	sinecatechins	D06BB12
	teduglutide	A16AX08
	tetrachlorodecaoxide	D03AX11
	vilazodone	N06AX24
	von Willebrand factor	B02BD10

ATC code changes:

INN/common name	Previous ATC	New ATC
alitretinoin	D11AX19	D11AH04
C1-inhibitor, plasma derived	B02AB03	B06AC01
icatibant	C01EB19	B06AC02

ATC name changes

Previous	New	ATC code
Agents for atopic dermatitis, excluding corticosteroids	Agents for dermatitis, excluding corticosteroids	D11AH
Other cold combination preparations	Other cold preparations	R05X

New DDDs:

INN/common name	DDD	Unit	Adm.R	ATC code
asenapine	20	mg	O	N05AH05
corifollitropin alfa	0.15	mg	P	G03GA09
dienogest	2	mg	O	G03DB08
eltrombopag	50	mg	O	B02BX05
fampridine	20	mg	O	N07XX07
flupirtine	0.4	g	O	N02BG07
indacaterol	0.15	mg	Inhal. powder	R03AC18
indometacin, combinations	0.1	g ¹	O,R	M01AB51
mifamurtide	0.7	mg	P	L03AX15
prucalopride	2	mg	O	A03AE04
roflumilast	0.5	mg	O	R03DX07
velaglucerase alfa	300	U	P	A16AB10

¹: refers to indometacin

Herbal medicinal products*

New ATC 5th level codes::

Name	ATC code
Horse chestnut, seeds	C05CX03

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

Recent Publications, Information and Events

Selection and use of medicines

World Health Organization — The 18th meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines took place in Accra, Ghana on 21–25 March 2011. The purpose of the meeting was to review and update the WHO Model List of Essential Medicines (EML) as well as the WHO Model List of Essential Medicines for Children (EMLc).

In accordance with its approved procedures, the Committee evaluated the scientific evidence on the comparative effectiveness, safety and cost effectiveness of medicines and updated the WHO Model List of Essential Medicines and the Model List of Essential Medicines for Children. The Committee:

- Approved the addition of 16 new medicines to the EML.
- Approved the deletion of 13 medicines from the EML.
- Approved new indications for 4 medicines already listed on the EML.
- Approved the addition of a new dosage form or strength for 4 medicines already on the EML.
- Rejected 9 applications for the addition of a medicine to EML.
- Approved the addition of 16 new medicines to the EMLc.
- Approved the deletion of 15 medicines from the EMLc,
- Rejected 3 applications for the addition of a new medicine to the EMLc.

Some of the main recommendations made, in order of their appearance on the EML, were:

- Section 6: addition of artesunate + amodiaquine combination tablet for the treatment of malaria in adults and children, in line with current WHO treatment guidelines. In making its decision, the 2011 Committee reviewed the latest clinical evidence and the information about licensing in several countries of the fixed dose combination tablet. The Committee noted that appropriate doses of both medicines can also be achieved using combinations of the mono-component products, including as co-blistered presentations.
- Section 10: addition of tranexamic acid injection for the treatment of adult patients with trauma and significant risk of ongoing haemorrhage. On the basis of the results of a very large trial of the use of tranexamic acid specifically for trauma patients — including those who have been in road traffic accidents, the Committee concluded that there is sufficient evidence to support the proposal that listing tranexamic acid may contribute to a reduction in this cause of death.
- Section 18.5 : addition of glucagon injection, 1 mg/ml to treat acute severe hypoglycaemia in patients with diabetes, to support efforts in many countries to ensure appropriate treatment of the increasing number of patients with diabetes. The Committee also recommended that careful attention be paid to the cost of procuring glucagon and noted that based on experience with other high cost medicines, such as

antiretrovirals, inclusion in the EML may help to contribute to a reduction in prices.

- Section 22.1: addition of misoprostol tablet, 200 micrograms for the prevention of post-partum haemorrhage, where oxytocin is not available or cannot be safely used. WHO guidelines currently recommend that in situations where oxytocin is not available, misoprostol can be used to prevent and treat post partum haemorrhage due to uterine atony.

Based on the evidence provided, the Committee considered that misoprostol can be safely administered to women to prevent post-partum haemorrhage by health workers trained in its use in the third stage of labour. The addition of misoprostol for the treatment of post-partum haemorrhage was not approved. The clinical trials that compare misoprostol to oxytocin in women who need treatment for post-partum haemorrhage show that misoprostol is not as effective as oxytocin. In addition, there is no evidence to support the safety and efficacy of the 800-microgram dose for treatment of post partum haemorrhage when given to women who have already received prophylactic misoprostol 600 micrograms orally. Countries need to work to make oxytocin available for treatment of women who are bleeding after delivery and misoprostol should only be used if there is no other option.

Other medicines that were added to the EML are: isoflurane, propofol, midazolam, clarithromycin, miltefosine, paclitaxel and docetaxel, bisoprolol, terbinafine cream/ointment, mupirocin cream/ointment, and atracurium.

A summary of reasons for all changes to the EML is in Section 1 of the report. All applications and documents considered by the Committee will remain available

on the web site for the meeting at http://www.who.int/selection_medicines/committees/expert/18/en/index.html.

The next update of the WHO Model List of Essential Medicines will take place in 2013.

Reference: Unedited report of the 18th meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines at http://www.who.int/medicines/publications/unedited_trs/en/index.html

Policy guidelines on controlled substances

World Health Organization — The WHO Access to Controlled Medicines Team has published “Ensuring balance in national policies on controlled substances: guidance for availability and accessibility for controlled medicines”. This book provides guidance on policies and legislation with regards to availability, accessibility, affordability and regulation of controlled medicines.

It includes 21 guidelines on various topics: content of drug control legislation and policy; authorities and their role in the system; policy planning for availability and accessibility; healthcare professionals; estimates and statistics; procurement, and nationally listed drugs. Each guideline is followed by an explanation and a description of the legal context. The Country Assessment Checklist enables the user to determine which guidelines still need to be worked on. A CD-ROM provides additional information.

The guidelines are currently available in English. Other on-line language versions will follow, some of them very soon (Armenian, Bulgarian, French, Georgian, Greek, Hungarian, Khmer, Polish, Russian, Serbian, Slovakian, Slovenian and Turkish). The publication will also become available in print in English and French.

Reference: Ensuring Balance in National Policies on Controlled Substances, Guidance for Availability and Accessibility of Controlled Medicines at: http://www.who.int/medicines/areas/quality_safety/guide_nocp_sanend/en/index.

List of medicines to save mothers and children

World Health Organization — The new document, “Priority medicines for mothers and children” contains a list of 30 medicines developed to advocate for better supply and use of the most important essential medicines. The vast majority of maternal and child deaths can be prevented when these 30 medicines are available in the right formulations and prescribed and used correctly.

Medicines on this new priority list were selected based on burden of disease data and their potential for impact on maternal and child mortality and morbidity. All medicines on the list are already in the WHO Model List of Essential Medicines and the latest WHO treatment guidelines. The list was developed by the Department of Essential Medicines and Pharmaceutical Policies (EMP) in collaboration with the Departments of Child and Adolescent Health and Development (CAH) and Making Pregnancy Safer (MPS), UNICEF and UNFPA.

Reference: *Priority medicines for mothers and children*, WHO/EMP/MAR/2011.1 at http://www.who.int/mediacentre/news/notes/2011/mother_child_medicine_20110321. The list can be downloaded at http://www.who.int/medicines/publications/emp_mar2011.1/en/index.html

World medicines situation

World Health Organization — The third edition of the “World Medicines Situation Report 2011” brings together new data on 24 key topics relating to pharmaceutical

production and consumption, innovation, regulation and safety.

Topics include selection, procurement, supply management, rational use, financing and pricing. Cross-cutting chapters cover household medicines use, access and human rights, good governance, human resources and national medicines policies.

The chapters released in April 2011 are:

- Background on past and present efforts to document and improve sharing of information.
- Medicines prices, availability and affordability featuring data and information from surveys using WHO standard methodology.
- Rational use of medicines describes the problem of bad practices in medicines prescribing and the harmful consequences in terms of morbidity, mortality and impact to health cost. This chapter looks at global data, and draws attention to trends in developing and transitional countries, in both public and private sectors.
- Traditional medicines: global situation issues and challenges describes use of traditional and herbal medicines around the world.
- Access to controlled medicines. International drug treaties stress that psychotropic and narcotic substances must be available for medical and scientific use, even if they are classified as controlled medicines.
- Good governance reviews the findings of country studies, highlighting weaknesses and strengths in pharmaceutical systems that can help policy-makers better understand problems and identify solutions.

Reference: *The World Medicines Situation Report 2011*, available at http://www.who.int/medicines/areas/policy/world_medicines_situation/en/index.html

Artesunate instead of quinine saves lives

Médecins sans Frontières (MSF) have released a report calling for a change in severe malaria treatment protocols from centuries old quinine use to the newer, more effective drug artesunate (1).

In its report "Making the Switch", MSF calls on African governments to follow World Health Organization (WHO) guidelines, and switch from the far less effective quinine to artesunate which could avert nearly 200 000 deaths each year.

For decades, quinine has been used in severe malaria but it can be both difficult to administer and dangerous. Artesunate is safer, easier and more effective than quinine. Quinine has to be given three times a day in a slow intravenous drip that takes four hours: a treatment that is burdensome for both patients and

health staff. Artesunate, in contrast, can be given in just four minutes as an intravenous or intramuscular injection.

A landmark clinical trial in late 2010 concluded that the use of artesunate to treat children with severe malaria reduces the risk of death by nearly a quarter. The study, carried out in nine African countries, found that for every 41 children given artesunate over quinine, one extra life was saved. Because of the complexities of administering quinine, children in the trial who were assigned to receive quinine were almost four times more likely to die before even receiving treatment.

MSF participated in the trial through its research affiliate Epicentre, with a research site in Uganda. MSF has since changed its own treatment protocols and now plans to work with national health authorities to roll out artesunate in its projects over the coming months.

Reference: Médecins sans Frontières. Making the Switch at <http://www.msf.org/msf/articles/2011/04/malaria-making-the-switch.cfm>

Consultation Documents

The International Pharmacopoeia

Revision of monograph on capsules

This monograph was adopted by the Forty-fourth WHO Expert Committee on Specifications for Pharmaceutical Preparations in October 2009 for addition to The International Pharmacopoeia.

Capsules

The requirements of this monograph do not necessarily apply to preparations that are intended for use other than by oral administration, such as vaginal or rectal capsules etc. Such preparations may require a special formulation, method of manufacture, or form of presentation appropriate to their particular use. Starch capsules (often known as cachets) are not included in this monograph.

Definition

Capsules are solid dosage forms with hard or soft shells. They are of various shapes and sizes and contain a single dose of one or more active ingredients. They are intended for oral administration.

Capsule surfaces may bear symbols or other markings.

Capsule shells are made of gelatin or other substances, the consistency of which may be modified by the addition of substances such as glycerol or sorbitol. The shell should disintegrate in the presence of digestive fluids so that the contents are released. The contents of capsules may be solid, liquid, or of a paste-like consistency. Capsule shells and contents may contain excipients such as diluents, solvents, surface-active substances, opaque fillers, antimicrobial agents, sweeteners, colouring matter authorized by the appropriate national or regional authority, flavouring substances, disintegrating agents, glidants, lubricants, and substances capable of modifying the behaviour of the active ingredient(s) in the gastrointestinal tract. The contents should not cause deterioration of the shell.

When excipients are used, it is necessary to ensure that they do not adversely affect the stability, dissolution rate, bioavailability, safety, or efficacy of the active ingredient(s); there must be no incompatibility between any of the components of the dosage form.

The different categories of capsule include hard capsules, soft capsules, and modified-release capsules [including delayed-release capsules (gastro-resistant/enteric capsules) and sustained-release capsules (extended-/prolonged-release capsules)].

Manufacture

The manufacturing and filling processes for capsules should meet the requirements of good manufacturing practices (GMP).

Very broad guidelines concerning the main critical steps to be followed during production of capsules, indicating those that are the most important, are provided below. Additional guidelines specific for hard or soft capsules are provided in the respective subsections below.

In the manufacture of capsules, measures are taken to:

- ensure that the active ingredient(s) when present in solid state form have appropriate solid-state properties such as particle-size distribution and polymorphic form;
- ensure that mixing with excipients is carried out in a manner that ensures homogeneity;
- minimize the degradation of the active ingredient(s);
- minimize the risk of microbial contamination, and
- minimize the risk of cross contamination.

The particle size of the active ingredient(s) may be of primary significance in determining the rate and extent of dissolution and the bioavailability of the drug product, especially for substances of low solubility in aqueous media. The uniformity of the final drug product is affected by the particle size of the active ingredient(s) as well as the excipients.

Throughout manufacturing, certain procedures should be validated and monitored by carrying out appropriate in-process controls. These should be designed to guarantee the effectiveness of each stage of production.

Packaging is required to be adequate to protect capsules from light when required, and from moisture and damage during transportation.

Visual inspection

Unpack and inspect at least 20 capsules. They should be smooth and undamaged. Evidence of physical instability is demonstrated by gross changes in physical appearance, including hardening or softening, cracking, swelling, mottling, or discoloration of the shell.

Uniformity of mass

Capsules comply with the test for 5.2 Uniformity of mass for single-dose preparations, unless otherwise specified in the individual monograph.

Uniformity of content

Where a requirement for compliance with the test for 5.1 Uniformity of content for single-dose preparations is specified in an individual capsule monograph, the test for 5.2 Uniformity of mass for single-dose preparations is not required.

Dissolution/disintegration

Where a choice of test is given (either test A or test B may be applied), follow the instructions in the monograph. Where a requirement for compliance with a dissolution test is specified in the individual monograph, the requirement for disintegration stated in the sections below do not apply.

Labelling

Every pharmaceutical preparation must comply with the labelling requirements established under GMP.

The label should include:

1. The name of the pharmaceutical product.
2. The name(s) of the active ingredient(s); International Nonproprietary Names (INNs) should be used wherever possible.
3. The amount of the active ingredient(s) in each capsule and the number of capsules in the container.
4. The batch (lot) number assigned by the manufacturer.
5. The expiry date and, when required, the date of manufacture.
6. Any special storage conditions or handling precautions that may be necessary.
7. Directions for use, warnings, and precautions that may be necessary.
8. The name and address of the manufacturer or the person responsible for placing the product on the market.

Storage

Capsules should be kept in well-closed containers. They should be protected from light when required, and from excessive moisture, or dryness, and should not be subjected to temperatures above 30 °C. Additional special packaging, storage, and transportation recommendations are provided, where necessary, in the individual monograph.

Requirements for specific types of capsules**Hard capsules****Definition**

Hard capsules have shells consisting of two prefabricated cylindrical sections that fit together. One end of each section is rounded and closed, and the other is open. The contents of hard capsules are usually in solid form (powder or granules).

Manufacture

Sometimes, the physical characteristics of the mixture of the active ingredient(s) and excipients allow it to be directly filled into the shell, but it may occasionally be necessary to granulate before filling. Normally the granulate needs to be mixed with lubricants and/or disintegrating agents. The use of excessive amounts of lubricants should be avoided since these may deleteriously affect the capsules.

In-process controls during hard capsule production should include the moisture content of the mixture and/or granulate (as well as of the shells), the size of granules, the flow of the final mixture, and the uniformity of mass, capsule size, integrity of the seals, and disintegration or dissolution rate (e.g., for modified-release capsules) of the finished dosage form.

Disintegration test

Hard capsules comply with 5.3 Disintegration test for tablets and capsules.

Use water as the immersion fluid unless hydrochloric acid (0.1 mol/l) VS or other medium is specified in the individual monograph. Operate the apparatus for 30 minutes, unless otherwise justified and authorized and examine the state of the capsules. If capsules float, use a disc as described under 5.3 Disintegration test for suppositories.

Soft capsules**Definition**

Soft capsules have thicker shells than hard capsules, and antimicrobial preservatives are usually added. The shells are of one piece and various shapes. The contents of soft capsules are usually solutions or suspensions of the active ingredient(s) in non-aqueous liquids. Partial migration of the contents into the shell may occur (and vice versa) depending on the nature of the materials used and the product in question.

Manufacture

Soft capsules are usually formed, filled, and sealed in one operation. However, shells for extemporaneous use are sometimes prefabricated. Liquids may be incorporated directly. Solids are usually dissolved or dispersed in a suitable excipient(s) to give a solution, suspension or dispersion of paste-like consistency.

In-process controls during soft capsule production should include the viscosity of the contents, and the uniformity of mass, capsule size, integrity of the seals, and disintegration or dissolution rate (e.g., for modified-release capsules) of the finished dosage form.

Disintegration test

Soft capsules comply with 5.3 Disintegration test for tablets and capsules, using water as the immersion fluid unless hydrochloric acid (0.1 mol/l) VS or other medium is specified in the individual monograph. Add a disc to each tube. Liquid active substances dispensed in soft capsules may attack the disc; in such circumstances and where authorized, the disc may be omitted. Operate the apparatus for 30 minutes and examine the state of the capsules. If the capsules fail to comply because of adherence to the discs, the results are invalid. Repeat the test on a further 6 capsules omitting the discs.

Modified-release capsules**Definition**

Modified-release capsules are hard or soft capsules in which the contents or the shell or both contain excipients or are prepared by special procedures such as micro-encapsulation which, separately or together, are designed to modify the rate, place or time of release of the active ingredient(s) in the gastrointestinal tract.

Sustained-release capsules (extended- or prolonged-release capsules)**Definition**

Sustained-release capsules are designed to slow the rate of release of the active ingredient(s) in the gastrointestinal tract.

All requirements for these specialized dosage forms are given in the individual monographs.

Delayed-release capsules (gastro-resistant/enteric capsules)

Definition

Delayed-release capsules are hard or soft capsules prepared in such a manner that either the shell or the contents resist the action of gastric fluid but release the active ingredient(s) in the presence of intestinal fluid.

Manufacture

The additional statements given under either hard or soft capsules apply, as appropriate to delayed-release capsules.

Disintegration test

Delayed-release capsules with a gastro-resistant shell comply with 5.3 Disintegration test for tablets and capsules, using hydrochloric acid (0.1 mol/l) VS as the immersion fluid. Operate the apparatus without the discs for 2 hours, unless otherwise specified in the individual monograph (but in any case for not less than 1 hour), and examine the state of the capsules. No capsule should show signs of disintegration or rupture permitting the contents to escape. Replace the acid by phosphate buffer solution, pH 6.8, TS with added pancreatin R where specified in the individual monograph. Add a disc to each tube. Operate the apparatus for 60 minutes and examine the state of the capsules. If the capsules fail to comply because of adherence to the discs, the results are invalid. Repeat the test on a further 6 capsules omitting the discs.

For capsules in which the contents, rather than the shell, resist the action of gastric fluid, carry out a suitable dissolution test to demonstrate the appropriate release of the active substance(s).

Revision of monograph on tablets

This monograph was adopted by the Forty-fourth WHO Expert Committee on Specifications for Pharmaceutical Preparations in October 2009 for addition to The International Pharmacopoeia.

Tablets

The requirements of this monograph do not necessarily apply to preparations that are intended for use other than by oral administration, such as implants, solution-tablets for injections and irrigations, tablets for external use, vaginal tablets, etc. Such preparations may require a special formulation, method of manufacture, or form of presentation, appropriate to their particular use.

Definition

Tablets are solid dosage forms usually obtained by single or multiple compression of powders or granules. In certain cases tablets may be obtained by moulding or extrusion techniques. They are uncoated or coated.

Tablets are normally right circular solid cylinders, the end surfaces of which are flat or convex and the edges of which may be bevelled. They may have lines or break-marks (scoring), symbols, or other markings.

If the break-mark(s) is/are intended to facilitate breaking the tablet for ease of swallowing a dose consisting of one or more whole tablets, the scoring is not critical. However, if the break-mark(s) is/are intended to permit accurate subdivision of the tablet in order to provide doses of less than one tablet, the scoring is critical. Tablets containing active ingredients having a narrow therapeutic window should generally not be presented with break-marks for subdivision. Non-functional break-marks should be avoided.

Tablets contain one or more active ingredients. They may contain excipients such as diluents, binders, disintegrating agents, glidants, lubricants, substances capable of modifying the behaviour of the dosage forms and the active ingredient(s) in the gastrointestinal tract, colouring matter authorised by the appropriate national or regional authority, and flavouring substances. When such excipients are used, it is necessary to ensure that they do not adversely affect the stability, dissolution rate, bioavailability, safety, or efficacy of the active ingredient(s); there must be no incompatibility between any of the components of the dosage form.

Tablets are single-dose preparations intended for oral administration. Some are intended to be swallowed whole, some after being chewed and some after being crushed, some are intended to be dissolved or dispersed in water before being taken and some are intended to be retained in the mouth where the active ingredient(s) is/are liberated.

The different categories of tablet include:

- uncoated tablets
- coated tablets (including film-coated and sugar-coated tablets)
- soluble tablets
- dispersible tablets
- effervescent tablets
- chewable tablets
- tablets for use in the mouth (including sublingual and buccal tablets)
- modified-release tablets (including delayed-release tablets (gastro-resistant/enteric-coated tablets) and sustained-release tablets (extended-/prolonged-release tablets)).

Manufacture

The manufacturing processes for tablets should meet the requirements of good manufacturing practices (GMP).

The following information is intended to provide broad guidelines concerning the critical steps to be followed during production of tablets.

In the manufacture of tablets, measures are taken to:

- Ensure that the active ingredient(s) have appropriate solid-state properties such as particle size distribution and polymorphic form.
- Ensure that mixing with excipients is carried out in a manner that ensures homogeneity.
- Ensure that the tablets possess a suitable mechanical strength to avoid crumbling or breaking on subsequent processing, e.g. coating, storage and distribution.
- Minimize the degradation of the active ingredient(s).
- Minimize the risk of microbial contamination.
- Minimize the risk of cross-contamination.

In addition, in the manufacture of those scored tablets (tablets bearing a break-mark or marks) for which subdivision is intended in order to provide doses of less than one tablet measures are taken to:

- Ensure the effectiveness of break-marks with respect to the uniformity of mass of the subdivided parts so that the patient receives the intended dose.

A suitable test to assess this aspect of product quality during development is as follows:

Take 30 tablets at random. Break each tablet by hand and take one part for the test and reject the other part(s). Weigh each of the 30 parts thus obtained and calculate the average mass. No individual mass is outside the limits of 75% to 125% and not more than one individual mass is outside the limits of 85% to 115% of the average mass.

The particle size of the active ingredient(s) may be of primary significance in determining the rate and extent of dissolution, the bioavailability, and the uniformity of a drug product, especially for substances of low solubility in aqueous media.

Sometimes, the physical characteristics of the mixture allow it to be directly compressed. In this case, the particle size distribution and flowability of the ingredients becomes particularly important because of the risk for segregation during handling of the mix. However, it is usually necessary to granulate before compression, preferably by wet-granulation but in certain cases dry-granulation or slugging may be preferred. Generally, wet-granulation of the mix before compression reduces the risk for segregation. When a wet-granulation technique is employed, control of the residual moisture after the drying step is important for smooth tablet compression. Too low or too high moisture contents may influence the chemical and physical stability of the final tablet. The granulate and powders normally need to be mixed with glidants and lubricants before the compression stage to improve the powder flow and to reduce sticking and adhesion to die walls and punches during compression. The use of excessive amounts of glidants and lubricants should be avoided since these will deleteriously affect the tablets. Some lubricants like magnesium stearate may in excessive amounts or by long mixing times reduce the mechanical resistance of tablets and prolong disintegration and dissolution time.

Throughout manufacturing, certain procedures should be validated and monitored by carrying out appropriate in-process controls. These should be designed to guarantee the effectiveness of each stage of production. In-process controls during tablet production should include the moisture content of the mixture and/or granulate, the size of granules, the flow of the final mixture and, where relevant, the uniformity of mass of tablet cores before coating. In-process controls during tablet production should also include the dimensions (thickness, diameter), uniformity of mass, hardness and/or crushing force, friability, disintegration, or dissolution rate (for example, for modified-release tablets) of the finished dosage form.

In the manufacture, packaging, storage and distribution of tablets, suitable measures are taken to ensure their microbiological quality.

Packaging is required to be adequate to protect the tablets from light, moisture, and damage during transportation.

The validation of the manufacturing process and the in-process controls are documented.

Visual inspection

Unpack and inspect at least 20 tablets. They should be undamaged, smooth, and usually of uniform colour.

Evidence of physical instability is demonstrated by:

- Presence of excessive powder and/or pieces of tablets at the bottom of the container (from abraded, crushed, or broken tablets).
- Cracks or capping, chipping in the tablet surfaces or coating, swelling, mottling, discoloration, fusion between tablets.
- The appearance of crystals on the container walls or on the tablets.

Uniformity of mass

Tablets comply with the test for 5.2 Uniformity of mass for single-dose preparations, unless otherwise specified below or in the individual monograph.

Uniformity of content

Where a requirement for compliance with the test for 5.1 Uniformity of content for single-dose preparations is specified in an individual tablet monograph the test for 5.2 Uniformity of mass for single-dose preparations is not required.

Dissolution/disintegration

Where a choice of test is given (either test A or test B may be applied), follow the instructions in the monograph. Where a requirement for compliance with a dissolution test is specified in the individual monograph, the requirements for disintegration stated in the sections below do not apply.

Labelling

Every pharmaceutical preparation must comply with the labelling requirements established under GMP.

The label should include:

1. The name of the pharmaceutical product.
2. The name(s) of the active ingredient(s); International Nonproprietary Names (INN) should be used wherever possible.
3. The amount of the active ingredient(s) in each tablet and the number of tablets in the container.
4. The batch (lot) number assigned by the manufacturer.
5. The expiry date and, when required, the date of manufacture.
6. Any special storage conditions or handling precautions that may be necessary.
7. Directions for use, warnings, and precautions that may be necessary.
8. The name and address of the manufacturer or the person responsible for placing the product on the market.

For scored tablets where the directions for use include subdivision to provide doses of less than one tablet, the label should also include:

9. The storage conditions for and period of use of those subdivided part(s) not immediately taken or administered.

Storage

Tablets should be kept in well-closed containers and protected from light, moisture, crushing, and mechanical shock. Tablets should be able to withstand handling, including packaging and transportation, without losing their integrity. Moisture-sensitive forms, such as effervescent tablets, should be stored in tightly closed containers or moisture-proof packs and may require the use of separate packages containing water-adsorbent agents, such as silica gel. Moisture-sensitive forms, such as effervescent tablets, should be stored in tightly closed containers or moisture-proof packs and may require the use of separate packages containing water-adsorbent agents, such as silica gel, or in unit dose packaging (blister cards).

Additional special packaging, storage, and transportation recommendations are provided, where necessary, in the individual monograph.

Requirements for specific types of tablets

Uncoated tablets

Definition

The majority of uncoated tablets are made in such a way that the release of active ingredients is unmodified. A broken section, when examined under a lens, shows either a relatively uniform texture (single-layer tablets) or a stratified texture (multilayer tablets), but no signs of coating.

Disintegration test

Uncoated tablets, except soluble tablets, dispersible tablets, effervescent tablets and tablets for use in the mouth comply with 5.3 Disintegration test for tablets and capsules. Operate the apparatus for 15 minutes, unless otherwise specified in the individual monograph, and examine the state of the tablets.

Soluble tablets**Definition**

Soluble tablets are uncoated or film-coated tablets that are intended to be dissolved in water giving a clear or slightly opalescent solution.

Disintegration test

Soluble tablets disintegrate within 3 minutes when examined by 5.3 Disintegration test for tablets and capsules, but using water R at 15–25 °C.

Dispersible tablets**Definition**

Dispersible tablets are uncoated tablets or film-coated tablets intended to be dispersed in water before administration giving a homogeneous dispersion.

Disintegration test

Dispersible tablets disintegrate within 3 minutes when examined by 5.3 Disintegration test for tablets and capsules, but using water R at 15–25 °C.
Fineness of dispersion

Place 2 tablets in 100 ml of water R and stir until completely dispersed. A smooth dispersion is produced, which passes through a sieve screen with a nominal mesh aperture of 710 µm.

Effervescent tablets**Definition**

Effervescent tablets are uncoated tablets generally containing acid substances and carbonates or hydrogen carbonates that react rapidly in the presence of water to release carbon dioxide. They are intended to be dissolved or dispersed in water before administration.

Manufacture

The manufacture of effervescent tablets is carried out in low-humidity conditions so that the reaction between acidic and basic components of the formulation does not take place.

Labelling

The label should state: "Not to be swallowed directly".

Disintegration test

Place one tablet in a 250 ml beaker containing 200 ml of water R at 15–25 °C. Numerous bubbles of gas are evolved. When the evolution of gas around the tablet or its fragments ceases, the tablet should have disintegrated, being either dissolved or dispersed in the water so that no agglomerates remain. Repeat the operation on five

additional tablets. The tablets comply with the test if each of the six tablets used in the test disintegrates within 5 minutes, unless otherwise specified in the individual monograph.

Chewable tablets

Definition

Chewable tablets are usually uncoated. They are intended to be chewed before being *swallowed*.

In the manufacture of chewable tablets, measures are taken to:

- Ensure that the tablets are easily crushed by chewing.
- Ensure that the tablets are palatable.

Tablets for use in the mouth (sublingual, buccal)

Definition

Tablets for use in the mouth are usually uncoated. They are usually formulated to effect a slow release and local action of the active ingredient(s) (for example, compressed lozenges) or the release and absorption of the active ingredient(s) under the tongue (sublingual tablets) or in other parts of the mouth (buccal) for systemic action.

Manufacture

In the manufacture of tablets for use in the mouth, measures are taken to:

- Ensure the release characteristics are appropriate to the intended use

Coated tablets

Definition

Coated tablets are tablets covered with one or more layers of mixtures of substances such as natural or synthetic resins, polymers, gums, fillers, sugars, plasticizers, polyols, waxes, colouring matters authorized by the appropriate national or regional authority, flavouring substances, and sometimes also active ingredients. A broken section, when examined under a lens, shows a core which is surrounded by a continuous layer of a different texture.

The tablets may be coated for a variety of reasons such as protection of the active ingredients from air, moisture, or light, masking of unpleasant tastes and odours, or improvement of appearance. The substance used for coating is usually applied as a solution or suspension.

Three main categories of coated tablet may be distinguished: sugar-coated, film-coated, and certain modified-release tablets.

Sugar-coated tablets

Uniformity of mass

The test for 5.2 Uniformity of mass for single-dose preparations, does not apply to sugar-coated tablets (see in-process controls under "Manufacture").

Disintegration test

Sugar-coated tablets comply with 5.3 Disintegration test for tablets and capsules. Operate the apparatus for 60 minutes, unless otherwise specified in the individual monograph, using water, and examine the state of the tablets. If any of the tablets has not disintegrated, repeat the test on an additional six tablets, using hydrochloric acid (0.1 mol/l) VS.

All six tablets must disintegrate.

Film-coated tablets**Definition**

A film-coated tablet is covered with a thin layer of resins, polymers, and/or plasticizers capable of forming a film.

Disintegration test

Film-coated tablets comply with 5.3 Disintegration test for tablets and capsules. Operate the apparatus for 30 minutes, and examine the state of the tablets.

Modified-release tablets**Definition**

Modified-release tablets are coated, uncoated, or matrix tablets containing excipients or prepared by procedures which, separately or together, are designed to modify the rate, the place or the time of release of the active ingredient(s) in the gastrointestinal tract.

Sustained-release tablets (Extended-/prolonged-release tablets)**Definition**

Sustained-release tablets are designed to slow the rate of release of the active ingredient(s) in the gastrointestinal tract.

All requirements for these specialized dosage forms are given in the individual monographs.

Delayed-release tablets (gastro-resistant/enteric-coated tablets)**Definition**

Delayed-release tablets are intended to resist gastric fluid but disintegrate in intestinal fluid. This is achieved by using coating substances such as cellacefate (cellulose acetate phthalate) and anionic copolymers of methacrylic acid and its esters. It is sometimes necessary to apply more than one layer.

Uniformity of mass

The test for 5.2 Uniformity of mass for single-dose preparations does not apply to delayed-release tablets.

Disintegration test

Delayed-release tablets comply with 5.3 Disintegration test for tablets and capsules, using hydrochloric acid (0.1 mol/l) VS as the immersion fluid. Operate the apparatus for 2 hours, unless otherwise specified in the individual monograph (but in any case

for not less than 1 hour), and examine the state of the tablets. No tablet should show signs of either disintegration (apart from fragments of coating) or cracks that would allow the contents to escape. Replace the acid by phosphate buffer solution, pH 6.8, TS. Operate the apparatus for 60 minutes and examine the state of the tablets.

Paediatric retinol oral solution

Draft proposal for *The International Pharmacopoeia* (February 2011). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Fax +41227914730 or e-mail to mendyc@who.int. A subscriber mailing list is now available to speed up consultation. For more information please contact bonnyw@who.int.

[Note from the secretariat: Paediatric retinol soft gel capsules in doses of 100 000 IU and 200 000 IU have a unique mode of delivery for use in public health programmes worldwide: unlike other capsules, these preparations are equipped with a nipple to be snipped before use. The dosage form is then squeezed and its content is delivered directly into the patient's mouth.]

WHO has developed a public standard which could be applicable to oral oily solutions in multidose dispensers as well as to single doses, each encapsulated in a soft gelatin shell.

Feedback is sought in particular about the proposed determination of the retinol content per delivered dose for single-dose containers. An alternative would be to determine the retinol content per single-dose container (capsule). The different approaches will influence the assay results as investigations have shown that about 10% of the material filled into soft capsules remain inside and is not actually delivered under the typical condition of use.]

Other name. Paediatric vitamin A oral solution.

Category. Vitamin.

Storage. Paediatric retinol oral solution should be kept in a tight, light-resistant, container.

Labelling. The labelling should state the name of the retinol ester or esters present, the proportion of vitamin A expressed in International Units (IU), and the names and proportions of any stabilizing agents added.

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

Oral oily solution in multidose dispenser: 100 000 IU/ml.

Oral oily solution as single-doses (capsules): 100 000 IU; 200 000 IU.

REQUIREMENTS

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

Definition. Paediatric retinol oral solution contains Retinol concentrate, oily form diluted in a suitable vegetable oil. It may contain suitable antimicrobial agents and stabilizing agents such as antioxidants. The oral solution contains not less than 90% and not more than 120% of the amount of vitamin A stated on the label.

Paediatric retinol oral solution may be presented either in a multidose container with a suitable administration device or as single doses, each encapsulated in a soft gelatin shell. The capsule shell is designed so that it may be broached (for example, with a nipple which may be cut) and so that the oral solution may be administered easily by mouth when the broached shell is squeezed gently.

Manufacture. For an oral solution presented as single doses, each encapsulated in a soft gelatin shell, the composition and method of manufacture of the soft gelatin shell and the packaging of the final product is chosen and/or validated to ensure that the contents can be adequately expressed with use of only gentle pressure.

Carry out the analytical procedures as rapidly as possible, avoiding exposure to actinic light and oxidizing agents, and maintaining whenever possible an atmosphere of nitrogen above the solutions.

Identity tests

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

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

A.1 Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 12 volumes of cyclohexane R and 1 volume of ether R as the mobile phase. Apply separately to the plate 2 µl of each of the following 4 solutions in cyclohexane R. For solution (A) dissolve a quantity of the oral solution containing the equivalent of 50 000 IU of vitamin A in 10 ml. For solution (B) prepare a solution of retinol acetate RS equivalent to 5000 IU of vitamin A per ml. For solution (C) prepare a solution of retinol propionate RS equivalent to 5000 IU of vitamin A per ml. For solution (D) prepare a solution of retinol palmitate RS equivalent to 5000 IU of vitamin A per ml. After removing the plate from the chromatographic chamber, allow it to dry in air, and examine the chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution (A) corresponds in position and appearance to one or more of the spots obtained with solutions (B), (C) and (D).

A.2 Carry out the test as described under 1.14.1 Thin-layer chromatography, using the conditions described above under test A.1 but using silica gel R5 as the coating substance. After removing the plate from the chromatographic chamber, allow it to dry in air and spray with antimony trichloride TS. Examine the chromatogram in daylight. The principal spot obtained with solution (A) corresponds in position and appearance to one or more of the spots obtained with solutions (B), (C), and (D).

B. Dissolve a drop of the oral solution in about 1 ml of dichloromethane R and add 5 ml of antimony trichloride TS; a blue colour is immediately produced which turns gradually to violet-red.

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

D. To a quantity of the oral solution containing the equivalent of 50 000 IU of vitamin A, add 100 ml of ethanol (~750 g/l) TS. Dilute 1 ml of the resulting solution to 50 ml with a mixture of 100 volumes of ethanol (~750 g/l) TS and 1 volume of hydrochloric acid (~420 g/l) TS. Immediately after preparation measure the absorbance (1.6) in the range 300 to 400 nm. The solution exhibits a single maximum at 326 nm. Heat the solution in a water bath for 30 seconds and cool rapidly. The absorption spectrum of the resulting solution, when observed between 300 and 400 nm, exhibits a shoulder at 332 nm and maxima at 348, 367 and 389 nm

Uniformity of deliverable dose (single-dose containers). For an oral solution presented in single-dose containers the individual mass of the expressed contents of at least 18 of the single-dose containers as weighed under Assay is within $\pm 10\%$ of the average mass and no individual mass is outside $\pm 20\%$.

[Note from the secretariat: feedback is sought on the proposed determination of the retinol content per delivered dose for single-dose containers. An alternative would be to determine the retinol content per capsule.]

Assay. For an oral solution presented in single-dose containers express the contents of 20 single-dose containers, following the directions for use as stated on the label. Weigh directly the individual contents delivered from each single-dose container and calculate the average mass. [Do not weigh the contents delivered by difference between full and empty containers.] Carry out the assay using the mixed oral solution from the 20 containers.

Either method A, where valid, or method B may be applied.

A. Immediately dissolve a quantity of the oral solution containing the equivalent of about 200 000 IU of vitamin A, accurately weighed, in 5 ml of n-pentane R and dilute with 2-propanol R to a presumed concentration of 10-15 IU per ml. Verify that the absorption maximum of the solution to be examined, against 2-propanol as blank, lies between 325 nm and 327 nm. Measure the absorbances at 300 nm, 326 nm, 350 nm and 370 nm. Calculate the ratio A_{λ}/A_{326} for each wavelength. If the ratios do not exceed 0.60 at 300 nm, 0.54 at 350 nm and 0.14 at 370 nm, calculate the content of vitamin A in IU.

For an oral solution presented in a multidose container calculate the content of vitamin A in IU per ml from the expression: $A_{326} \times V \times d \times 1900 / (100 \times m)$, where A_{326} is the absorbance at 326 nm, V is the total volume used for the dilution to give 10–15 IU per ml, m is the mass of sample used in g, d is the weight per ml (1.3.1) of the oral solution and 1900 is the factor to convert the specific absorbances of esters of retinol into IU per g.

For an oral solution presented as single doses calculate the deliverable content of vitamin A in IU per capsule from the expression: $A_{326} \times V \times d \times 1900 / (100 \times m)$, where A_{326} is the absorbance at 326 nm, V is the total volume used for the dilution to give 10-15 IU per ml, m is the mass of sample used in g, AM is the average mass of the expressed contents in g per capsule and 1900 is the factor to convert the specific absorbances of esters of retinol into IU per g.

If one or more of the ratios A_{λ} / A_{326} exceeds the values given, or if the wavelength of the absorption maximum does not lie between 325 nm and 327 nm, use Method B.

B. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (15 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with octadecylsilyl groups (5 μ m). As the mobile phase, use a mixture of 95 volumes of methanol R and 5 volumes of water R. Prepare the following solutions. For solution (1) transfer a quantity of the oral solution containing the equivalent of about 100 000 IU of vitamin A, accurately weighed, into a 100 ml volumetric flask. Dissolve immediately in 5 ml of n-pentane R. Add 40 ml of 0.1 M tetrabutylammonium hydroxide TS in 2-propanol R. Swirl gently and allow the mixture to stand for 10 minutes at a temperature between 60 ° and 65 °C, swirling occasionally. Allow to cool to room temperature, dilute to volume with 2-propanol R containing 1 g/l butylated hydroxytoluene R, and homogenise carefully to avoid air bubbles. Dilute 5 ml of the resulting solution to 50 ml with 2-propanol R. For solution (2) transfer an amount of retinol acetate RS or retinol palmitate RS containing about 100 000 IU of vitamin A, accurately weighed, into a 100 ml volumetric flask. Proceed as described for solution (1).

Operate with a flow rate of 1 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 325 nm.

Inject alternately 10 μ l each of solutions (1) and (2) and record the chromatograms for 1.5 times the retention time of retinol.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2). Determine the weight per ml (1.3.1) and calculate the content of vitamin A in IU per ml of the oral solution or, where appropriate, in IU delivered per capsule.