

WHO Drug Information

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Drug Management

Avian influenza: impact on health programmes

Avian influenza is an infectious disease of birds caused by type A strains of the influenza virus. The disease, which was first identified in Italy more than 100 years ago, occurs worldwide.

All birds are thought to be susceptible to infection with avian influenza, though some species are more resistant to infection than others. Infection causes a wide spectrum of symptoms in birds, ranging from mild illness to a highly contagious and rapidly fatal disease resulting in severe epidemics. The latter is known as “highly pathogenic avian influenza”. This form is characterized by sudden onset, severe illness, and rapid death, with a mortality that can approach 100%.

Fifteen subtypes of influenza virus are known to infect birds, thus providing an extensive reservoir of influenza viruses potentially circulating in bird populations. To date, all outbreaks of the highly pathogenic form have been caused by influenza A viruses of subtypes H5 and H7.

A constantly mutating virus

All type A influenza viruses, including those that regularly cause seasonal epidemics of influenza in humans, are genetically labile and well adapted to elude host defenses. Influenza viruses lack mechanisms for the “proofreading” and repair of errors that occur during replication. As a result of these uncorrected errors, the genetic composition of the viruses changes as they replicate in humans and animals, and the existing strain is replaced with a new antigenic variant. These constant, permanent and usually small changes in the antigenic composition of influenza A viruses are known as antigenic “drift”.

The tendency of influenza viruses to undergo frequent and permanent antigenic changes necessitates constant monitoring of the global influenza situation and annual adjustments in the composition of influenza vaccines.

Influenza viruses have a second characteristic of great public health concern: influenza A viruses,

including subtypes from different species, can swap or “reassort” genetic materials and merge. This reassortment process, known as antigenic “shift”, results in a novel subtype different from both parent viruses. As populations will have no immunity to the new subtype, and as no existing vaccines can confer protection, antigenic shift has historically resulted in highly lethal pandemics. For this to happen, the novel subtype needs to have genes from human influenza viruses that make it readily transmissible from person to person for a sustainable period.

Conditions favourable for the emergence of antigenic shift have long been thought to involve humans living in close proximity to domestic poultry and pigs. Because pigs are susceptible to infection with both avian and mammalian viruses, including human strains, they can serve as a “mixing vessel” for the scrambling of genetic material from human and avian viruses, resulting in the emergence of a novel subtype. Recent events, however, have identified a second possible mechanism. Evidence is mounting that, for at least some of the 15 avian influenza virus subtypes circulating in bird populations, humans themselves can serve as the “mixing vessel”.

Clinical course and treatment of human cases of H5N1 avian influenza

Tests for diagnosing all influenza strains of animals and humans are rapid and reliable. Many laboratories in the WHO global influenza network have the necessary high-security facilities and reagents for performing these tests as well as considerable experience (<http://www.who.int/csr/>). Rapid bedside tests for the diagnosis of human influenza are also available, but do not have the precision of the more extensive laboratory testing that is currently needed to fully understand the most recent cases and determine whether human infection is spreading, either directly from birds or from person to person.

Antiviral drugs, some of which can be used for both treatment and prevention, are clinically effective against influenza A virus strains in otherwise healthy adults and children, but have some limitations. Some of these drugs are also expensive and supplies are limited.

Experience in the production of influenza vaccines is also considerable, particularly as vaccine composition changes each year to match changes in circulating virus due to antigenic drift. However, at least four months would be needed to produce a new vaccine in significant quantities, capable of conferring protection against a new virus subtype.

Influenza antiviral medicinal products for potential use during a pandemic*

Occasionally, emerging influenza A virus strains undergo major changes in their genes, especially in the neuraminidase (NA) and haemagglutinin (HA) genes. This may be due to an adaptation of an avian or porcine strain to the human host or to a genetic reassortment in a coinfection setting. The changes may provide the virus means for both increased infectivity and altered tissue distribution as well as a possibility to avoid detection by the host immune defence. Therefore, the new strains may have the capacity of causing severe worldwide pandemics. It is also possible that the past pandemic strains will re-emerge after being dormant for decades.

An influenza pandemic is a major acute threat to public health and warrants a concerted action for pandemic preparedness within the European Union. A wider international collaboration under the auspices of WHO is crucial for the proper surveillance and timely execution of pandemic plans. Influenza antiviral medicinal products and pandemic influenza vaccines have a complementary role in the management of an influenza pandemic. In contrast to pandemic vaccines, influenza antivirals can be used from the very early phase of an influenza pandemic.

In May 2004, the Committee for Human Medicinal Products (CHMP) of the European Medicines Agency (EMA) compiled and reviewed scientific information on antiviral medicinal products for use during an influenza pandemic. The CHMP conducted the review on the basis of information obtained from marketing authorization holders for amantadine, oseltamivir and zanamivir and from the literature. The recommendations were

* Review published by the European Medicines Agency (EMA), 7 Westferry Circus, Canary Wharf, London, E14 4HB, United Kingdom. Document EMA/CHMP/339972/2005. London, 27 October 2005. <http://www.emea.eu.int>

discussed in a workshop with European Experts held in February 2005. The review and its recommendations were submitted to the Commission in March 2005. The consensus reached at that time is summarized below.

It should be noted that by no means should any of the following scientific guidance on the use of antivirals in a pandemic situation be regarded as introducing derogation(s) to the terms of existing marketing authorisation.

Overview of available antivirals

There are four potential antiviral agents for the widespread use during an influenza pandemic, M2 inhibitors amantadine and rimantadine as well as the neuraminidase inhibitors oseltamivir and zanamivir.

Adamantane class (M2 inhibitors)

Rimantadine

Rimantadine inhibits the M2 membrane protein ion channel activity. This results in inhibition of the acidification of the virus interior which is required to promote fusion of the viral envelope with the endosome and for dissociation of the M1 matrix protein from the ribonucleoprotein complex (uncoating). Consequently, viral replication is blocked at an early stage of infection. Other effects may occur at later stages of the virus replication cycle.

Amantadine and rimantadine differ significantly in their pharmacokinetics, with rimantadine achieving higher concentrations in respiratory secretions. The peak plasma concentration is obtained after 6 hours of oral administration in healthy adults. The single dose elimination half-life in this population is about 25 hours. In healthy elderly people, the elimination is somewhat prolonged and the average AUC values and peak concentration is 20 to 30 % higher than in healthy adults.

Following oral administration, rimantadine is extensively metabolised in the liver with less than 25% of the dose excreted in the urine unchanged. In chronic liver disease, the pharmacokinetics of rimantadine are not appreciably altered, but in severe hepatic disorders, AUC and elimination half-life increase as apparent clearance is remarkably reduced. Renal insufficiency results in an increase in plasma metabolite concentrations and reduces apparent clearance of rimantadine.

Rimantadine does not interfere with the immunogenicity of inactivated influenza A vaccine. Interactions with other drugs like cimetidine, paracetamol (acetaminophen) and aspirin lead to only minor changes in the pharmacokinetics of rimantadine but are mentioned in the official labelling of Flumadine® (rimantadine, registered in USA). The extent to which interaction studies have been performed remains unknown. Flumadine® is contraindicated in patients with known hypersensitivity to drugs of the adamantane class, including rimantadine and adamantane.

Rimantadine is known to cross the placenta in mice and to be embryotoxic in rats at a high dose level. There are no adequate and well-controlled studies in pregnant women. Therefore, according to the Flumadine® label, rimantadine should be used during pregnancy only if the potential benefit justifies the risk to the foetus. However, without the possibility to assess the risk to the foetus, a recommendation to use rimantadine in pregnancy even during a pandemic is not possible. Rimantadine should not be administered to nursing mothers.

Efficacy data

According to a Cochrane review, 11 treatment trials were published between 1968 and 1986. The trials were analysed by using the duration of fever (defined as a temperature of more than 37 °C) as the common outcome measure. Compared to placebo, rimantadine significantly shortened the duration of fever by 1.27 days (95 % CI 0.77 to 1.77). The scarce available data suggest that amantadine and rimantadine have a comparable efficacy.

The Cochrane review identified several reports published between 1966 and 1990 on the prophylactic use of rimantadine. The study results were analysed according to the comparison of oral rimantadine to placebo and oral amantadine to oral rimantadine. Comparisons were stratified on the basis of whether participants had received vaccination or not. Rimantadine prevented 72 % (95 % CI –8% to 92 %) of influenza and 35 % (95 % CI –20 to 65 %) of influenza-like illnesses. Whilst these results were not statistically significant ($p = 0.07$ and $p = 0.17$, respectively), the estimates were based on only 688 individuals, and are of very similar magnitude to those for amantadine. Rimantadine seemed efficacious also in the vaccinated population. When comparing amantadine and rimantadine, there was no evidence of a difference in efficacy.

Sensitivity of different influenza strains

Rimantadine has no effect on influenza type B virus infection. The in vitro susceptibility covers the three antigenic subtypes, i.e., H1N1, H2N2, H3N2, that have been isolated from man.

Viral resistance

Amino acid replacement in the transmembrane domain of M2 leads to resistance to amantadine and rimantadine. Such rimantadine-resistant strains of influenza A have emerged among freshly isolated epidemic strains in closed settings where rimantadine has been used, but such strains have only rarely been isolated from specimens collected as part of routine influenza surveillance. Resistant viruses have been shown to be transmissible and to cause typical influenza illness. Analyses of some of the 2004 H5N1 viruses isolated from poultry and humans in Asia have shown that the viruses were resistant to amantadine and rimantadine.

Adverse effect profile

Rimantadine lacks the central nervous system effects seen with amantadine. The pharmacokinetic properties of rimantadine may account for its more favourable side effect profile compared to amantadine. The adverse effect profile of rimantadine includes the gastrointestinal system, the skin and the respiratory tract.

Regulatory status

Medicinal products containing rimantadine have been approved nationally. It should be noted that no information was provided by the marketing authorization holders (MAHs) of rimantadine within EU for the purpose of this assessment.

Amantadine

Amantadine inhibits the M2 membrane protein ion channel activity. This results in inhibition of the acidification of the virus interior which is required to promote fusion of the viral envelope with the endosome and for dissociation of the M1 matrix protein from the ribonucleoprotein complex (uncoating). Consequently, viral replication is blocked at an early stage of infection. Other effects may occur at later stages of the virus replication cycle.

Amantadine is absorbed well with oral bioavailability of 62–93% in the young and 53–100% in the elderly, based on published data. The time to attain peak plasma concentrations varies from 2 to 6 hours and the elimination half-life is relatively long, 12–16h.

Amantadine is not metabolised and is excreted unchanged in urine. Thus, the plasma half-life of amantadine is considerably prolonged in patients with impaired renal function (justifying dose adjustment in case of renal impairment) and the half-life of amantadine in elderly men after multiple doses is almost double that in young men. Average half-lives of 8.3 and 13 days have been recorded in patients on chronic haemodialysis.

Interactions with anticholinergic agents, several classes of medicinal products affecting CNS, combination diuretics, as well as with quinine and quinidine have been described. The product information on interactions may differ among the member states. Amantadine does not impair the immune response to the conventional influenza vaccine. The effect on (live) influenza vaccination is unknown.

Amantadine has not been studied in pregnant women. According to marketing authorization holders, there is no evidence of malformations or foetal toxicity due to amantadine in humans. However, claims of isolated reports on malformations have appeared in the literature although causality remains unknown. Anyway, based on animal embryotoxicity and teratogenesis studies, the use of amantadine is not recommended during pregnancy. Amantadine is not recommended during lactation because the drug is excreted into human breast milk.

Efficacy data

Only limited clinical information is available. Most of the clinical trials were performed between 1960 and 1980. Thus, these studies have neither been conducted nor assessed according to current regulatory standards. The assessment is mainly based on the Cochrane review "Amantadine and rimantadine for preventing and treating influenza A in adults updated in 2004".

Influenza A treatment indication of amantadine in the EU varies between the member states. The treatment (and prophylaxis) indication is for adults, adolescents and children or for adults and adolescents only, depending on the member state.

The recommended dose varies from 200 mg daily for healthy adults to 50–100mg daily for children. The dose is adjusted according to the renal function. The recommended duration is up to 10 days for treatment and up to 8 weeks for prophylaxis. Amantadine treatment of adults without concomitant diseases is estimated to shorten the

disease with fever by approximately one day. Data on the use in patients with chronic diseases are scarce. There is no strong evidence for the prevention of influenza-associated complications. Amantadine will not impair the efficacy of conventional influenza vaccines. No data on the use of amantadine for treatment of pandemic influenza were submitted for review by the Committee on Human Medicinal Products (CHMP).

The indication for prophylaxis for amantadine varies within the EU. Amantadine is often recommended for patients with risk factors for influenza complications. The recommended daily dose for prophylaxis is the same as for treatment but the dosing is for longer periods. In the pooled analysis of all placebo-controlled studies of prophylaxis, the protection against influenza was approximately 61%. Data of the use of amantadine for prophylaxis of influenza A in children were of questionable quality.

Sensitivity of different influenza strains

Amantadine inhibits human H1N1, H2N2 and H3N2 subtypes of influenza A. Amantadine (as well as rimantadine) does not inhibit influenza B. Antiviral activity has been demonstrated in vitro in cell culture at concentrations from 0.01 to 1.5 mg/ml (0.05–7.5 mM).

Amantadine has been used for prophylaxis during pandemics in 1968, caused by the H3N2, and in 1977 caused by the H1N1 influenza virus strain.

Avian and equine subtypes of influenza A are also sensitive. Recent H5N1 strains of "bird flu" are resistant to M2 inhibitors (amantadine and rimantadine). The level of phenotypic resistance is high, usually with > 100-fold reductions in susceptibility.

Viral resistance

In human influenza viruses, resistance is due to point mutation in the M gene. It has been also observed that a co-infection in mice with a mixture of amantadine-resistant and amantadine-sensitive strains of influenza virus resulted in the transfer of amantadine-resistance to a sensitive strain by reassortment.

It has been estimated that the overall frequency of phenotypic amantadine resistance for both H1N1 and H3N2 among influenza virus isolates in the UK 1968–1999 was 2.3%. In mice and chicken, resistance was obtained after one to three passages. In humans, the influenza A virus resistance to amantadine (rimantadine) occurs within 2 to 5 days of treatment, illustrating the

rapidity with which resistant virus can replace sensitive virus during treatment. Drug resistant virus appears when amantadine is used for treatment in about 30% of patients. Limited data show that drug-resistant virus was higher in treated children (up to 80%). This may be related to more intense and prolonged virus replication in children, which could be due to the absence of pre-existing immunity.

Amantadine (and rimantadine)-resistant viruses are able to transmit the disease. Amantadine-resistant viruses are cross-resistant to rimantadine and vice versa. Cross-resistance with the neuraminidase inhibitors does not occur.

Clinical significance of resistant strains

Resistant viruses can transmit the disease but have not been found to be more virulent than sensitive ones. Transmission of resistant strains can result in failures of influenza prophylaxis in family members and in nursing home contacts. The frequency of amantadine prophylaxis failures proven to be due to resistant variants in nursing home outbreaks in published studies was 0.5–2.4%. The increasing use of amantadine in China raises further concerns as regards the emergence of amantadine-resistant variants. Prolonged shedding of drug-resistant influenza virus in a hospital setting may have implications in terms of nosocomial infections.

Adverse effect profile and contraindications

The product information varies between the member states. In France, the product information mentions the following common adverse effects: dizziness, insomnia and nervousness. More rarely depression, anxiety, hallucination, confusion, nausea, anorexia, dry mouth, constipation, ataxia, orthostatic hypotension, headache are noted. Livedo reticularis and peripheral oedema have been observed in prolonged treatment. Exceptionally psychosis, urinary retention, dyspnoea, fatigue, rash, vomiting, weakness, slurred speech, vision disorders, convulsions, leucopenia, neutropenia, eczema, oculogyric episodes occurred. In France, amantadine is contraindicated in the following situations: hypersensitivity, concomitant use with neuroleptic anti-emetic drugs is contraindicated due to antagonism effect, children below one year of age due to the absence of specific data, and pregnancy due to the lack of clinical experience. The marketing authorization holder also contraindicates as follows: hypersensitivity to the product, severe renal failure, history of convulsions, history of gastric ulcerations, and severe heart disease.

Quality aspects related to pandemic use

The only available possibility for stockpiling would be the authorized formulation (tablets). No information on the preparation of a magistral formulation is known. It seems that amantadine bulk material itself shows excellent stability, but this needs to be further confirmed by reliable stability data. The current shelf life of the film coated tablets is 5 years, when stored below 25 °C.

Regulatory status

Medicinal products containing amantadine have been approved nationally.

B. Neuraminidase inhibitors

Oseltamivir

Used as treatment of influenza in adults and children one year of age or older who present with symptoms typical of influenza, when influenza virus is circulating in the community. Post exposure prevention in adults and adolescents 13 years of age or older following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community.

The appropriate use of oseltamivir for prevention of influenza should be determined on a case by case basis by the circumstances and the population requiring protection. In exceptional situations (e.g. in case of a mismatch between the circulating and vaccine virus strains, and a pandemic situation) seasonal prevention could be considered in adults and adolescents 13 years of age or older.

Oseltamivir (Tamiflu®) has been shown to be effective in post-exposure prophylaxis in children older than one year although a regulatory approval for the use in the paediatric population is still pending in the EU. The safety and efficacy of Tamiflu® in children less than one year of age have not been established.

For treatment of adults and adolescents 13 years or older as well as for children weighing more than 40 kg, the recommended oral dose is 75 mg oseltamivir twice daily, for 5 days. For children weighing 40 kg or less, the dosing is modified by weight.

In individuals at 13 years or older the recommended dose of oseltamivir for prevention of influenza following close contact with an infected individual is 75 mg oseltamivir once daily for at least 7 days.

The recommended dose for prevention of influenza during a community outbreak is 75 mg oseltamivir once daily for up to six weeks.

Pharmacology

Oseltamivir phosphate is an orally administered prodrug that, after absorption in vivo, is metabolised into oseltamivir carboxylate (OC), the clinically active metabolite. OC binds to highly conserved amino acid residues in the active site of neuraminidase, which is one of the two major surface glycoprotein antigens of influenza viruses. In influenza-infected host cells, newly formed viruses are transported to the cell membrane. The progeny viruses remain attached to the cell membrane until they are cleaved from the surface by the proteolytic activity of the viral neuraminidase. Prevention of this neuraminidase activity results in clustering of the newly formed viruses onto the surface of the host cells, thereby preventing further transmission of the viruses into adjacent cells. Prevention of the neuraminidase activity therefore effectively interrupts the virus life cycle and eventually aborts the influenza infection.

The absolute bioavailability of active oseltamivir after oral administration of the prodrug is 74–85%. There is no significant effect of food on the oral bioavailability of oseltamivir. The T_{max} of the active drug is 1.5–5h. The estimated average volume of distribution of the active metabolite of oseltamivir is 23–26 L, a volume equivalent to extra cellular body fluid. Thus, oseltamivir carboxylate is distributed to the potential sites of influenza virus replication. The binding of the oseltamivir carboxylate to human plasma protein is negligible.

Conversion of the prodrug to the active metabolite is predominantly due to hepatic esterase activity. No further metabolism of the parent or active molecules has been detected in man, and the in vitro studies indicated no interaction with cytochrome P450 isoenzymes. oseltamivir carboxylate (the active compound) has a mean apparent elimination half-life of 6.3 h. Oseltamivir is eliminated mainly via kidneys in the form of the active drug. The average C_{max} and AUC are lower in children as compared to adults. Pharmacokinetic studies of oseltamivir in the elderly have shown that plasma concentrations of the prodrug and the active drug were similar to those of younger adults.

Accumulation of active oseltamivir is seen in patients with decreased renal function. A three-fold increase in AUC is seen in individuals with a

creatinine clearance of < 30 ml/min and two-fold in individuals with a clearance of 31–60 ml/min.

No significant interactions have been demonstrated between oseltamivir and any other substances investigated. Similarly, oseltamivir will not interact with vaccination with the inactivated intramuscularly administered vaccine. Theoretically, the use of oseltamivir concomitantly with vaccination with the live intranasally administered vaccine could impair the immunogenicity of the vaccine, but no data on such an interaction are available.

Efficacy data

• Treatment

In a pooled analysis of the placebo-controlled clinical trials, the time to alleviation of illness was reduced by approximately one day among the oseltamivir recipients (100.6 h versus 124.5 h) when the treatment was started within 36 h of the onset of symptoms. The median duration of fever was reduced by 36% (44 h versus 69 h). Oseltamivir treatment has been shown to result in significant shortening of the period to cessation of virus shedding.

Subgroup analyses of clinical trials have shown that oseltamivir significantly reduces the duration of illness with the exception of patients with chronic co-morbid diseases. Oseltamivir is effective irrespective of the influenza vaccination status of the patients. In children, the median duration of influenza illness was reduced by 26% (101 h versus 137 h) when oseltamivir treatment was started within 48 h of the onset of illness. In a pooled analysis of all placebo-controlled trials among adults and adolescents, oseltamivir has been shown to reduce the incidence of influenza-related lower respiratory tract infections (mainly bronchitis) resulting in antibiotic therapy by 55% (4.6% versus 10.3%), and overall antibiotic use for any reason by 27% (14.0% versus 19.1%). Hospitalization for any cause was reduced among the oseltamivir recipients (0.7% versus 1.7%). In children aged 1–12 years, oseltamivir treatment reduced the development of acute otitis media as a complication by 44% (12% versus 21%). The incidence of antibiotic prescriptions was also significantly lower among oseltamivir recipients than among the placebo recipients (31% versus 41%).

Treatment of pandemic and/or avian influenza

There are no data on the use of oseltamivir in a real pandemic situation. Very limited data are

available on the use of oseltamivir for treatment of influenza caused by H5N1 strains that are related to the potential pandemic strains. In animal studies, the efficacy of oseltamivir has been demonstrated against H5N1 viruses that circulated in Hong Kong in 1997. No animal data are available on the efficacy of oseltamivir against the recent drifted strains of H5N1 viruses. However, in vitro studies indicate that oseltamivir is likely to be effective also against the current strains of H5N1 viruses and other avian viruses with a pandemic potential (e.g. H9N2, H7N7). Animal studies have also indicated that the avian influenza viruses may be shed for longer periods than normal epidemic viruses. If true during a pandemic, there would be a need to use oseltamivir for longer periods than 5 days for treating the patients.

• Prophylaxis

Oseltamivir is indicated for the prophylaxis of influenza in adults and children aged 13 years and older. Oseltamivir administered once daily has been shown to be effective both in seasonal prophylaxis among healthy persons and in post-exposure prophylaxis within families. In seasonal prophylaxis, the duration of medication has been up to 6 weeks, and in the post-exposure prophylaxis it has been 7–10 days.

In seasonal prophylaxis among healthy adults, the protective efficacy of oseltamivir against laboratory-confirmed influenza was 74%, and against culture-proven influenza 87%. Even higher protection was observed in a study of 6-week seasonal prophylaxis among frail elderly subjects in residential home care setting; the protective efficacy against laboratory-confirmed influenza was 92%. In addition, the protective efficacy among elderly persons who had been vaccinated against influenza was 91%.

In post-exposure prophylaxis in the family setting, the overall protective efficacy of oseltamivir among the contacts (aged >12 years) of an influenza-positive index case was 89%. In another postexposure prophylaxis study that included also children aged 1 year or older, the protective efficacy was 68%.

Impact on non-clinical infections, infectivity and immunogenicity

An important feature of oseltamivir prophylaxis is that it does not prevent influenza infection per se, but works by preventing further transmission of newly formed viruses into adjacent cells. Therefore, oseltamivir prophylaxis does not suppress

the antibody response to influenza infection if a subject acquires influenza during the prophylactic period.

Experience on pandemic use/ use for avian influenza

There are no data on the use of oseltamivir prophylaxis in a real pandemic situation. There are no properly controlled clinical studies in humans with respect to the current avian influenza strains. The prophylactic efficacy of oseltamivir was tested recently against a 2004 clinical isolate of the current avian influenza strain in a mouse model of influenza and significantly reduced the mortality against a lethal challenge of the virus at a dosage equivalent to the approved human dose. Survival was increased further with a prolonged treatment regimen. During the 2003 avian influenza H7N7 outbreak in the Netherlands, oseltamivir prophylaxis with the recommended dose of 75 mg once daily seemed to be effective to protect poultry workers and their close contacts.

Sensitivity of different influenza strains

Nine different types of influenza neuraminidases (N1–N9) are currently known to exist. With few exceptions, only influenza viruses with N1 and N2 have circulated among humans during the past century. In addition to documented efficacy against strains with N1 or N2, oseltamivir has been shown to be potent in vitro against influenza virus neuraminidases N3–N9.

Three distinct influenza pandemics occurred in the 20th century. The most devastating of them was the pandemic of 1918–20. This pandemic was caused by an H1N1 influenza virus. Oseltamivir has been shown to effectively inhibit recombinant influenza viruses possessing the haemagglutinin and neuraminidase of the 1918 strains of influenza both in vitro and in vivo in mice. The other pandemic strains H2N2 (1957), H3N2 (1968), and H1N1 (1977) are also inhibited in vitro and/or in vivo by oseltamivir.

In vitro, oseltamivir has been shown to be effective against H5N1 strains isolated during the initial human outbreak in Hong Kong in 1997 as well as recently (in 2004) isolated H5N1 strains in Vietnam. In vivo, the efficacy of oseltamivir against H5N1 viruses has been demonstrated mainly in a mouse model of influenza infection. Orally administered oseltamivir effectively prevented the death of mice infected with H5N1/97 viruses and recently oseltamivir prevented the death of mice infected with H5N1/04, obtained

from a clinical case in Vietnam. Oseltamivir treatment has also been shown to reduce mortality in chickens infected with another highly pathogenic avian influenza strain, H7N7, which recently caused a human outbreak in the Netherlands.

Viral resistance

Viral resistance to oseltamivir may develop by alteration of the amino acid composition of neuraminidase. Resistant strains have been generated *in vitro* and such strains have also been found in a small proportion of patients during or after treatment with oseltamivir. Oseltamivir-resistant strains have also been detected in individuals not exposed to oseltamivir. Mutations in the viral neuraminidase gene can be generated *in vitro* by repeated passages in the presence of low concentrations of oseltamivir. In clinical trials among adults and children older than 13 years, the incidence of development of resistant strains has been very low, 0.33%. However, in studies among children, the corresponding rate has been 4.0%–18%. The high rate of oseltamivir-resistance in children treated with oseltamivir is of concern and should be monitored carefully.

Clinical significance and surveillance of resistant strains

For the time being, the clinical significance of oseltamivir-resistant strains of influenza appears to be limited because of reduced infectivity, replicative ability, and pathogenicity of the resistant strains. The significance of the resistant strains observed in individuals who were not exposed to oseltamivir is unclear at the present. The decreased virulence and low rates of transmission have been shown in the ferret and mouse models with resistant strains carrying the mutation R292K or H274Y. With respect to the E119V mutation, the results are conflicting. Some studies in mice and ferrets have demonstrated a low infectivity of the resistant strain, but in a recent ferret study the infectivity and transmissibility of the resistant strain was comparable with the wild-type strain. No data are yet available for the newly detected resistant strain with the N294S mutation. The development of viral resistance is possible and might have a substantial impact on the clinical usefulness of oseltamivir. Therefore, a global surveillance network called the Neuraminidase Inhibitor Susceptibility Network (NISN) has been set up in collaboration with the World Health Organization (WHO) to monitor the possible emergence of viral resistance. The NISN monitors the situation globally, with particular emphasis on

countries in which the neuraminidase inhibitors are used most frequently.

Adverse effect profile and contraindications

Hypersensitivity to oseltamivir is the only listed contraindication. The most frequently reported adverse effects during oseltamivir treatment both in adults and children are nausea and vomiting. In pre-licensing clinical trials, the rate of these adverse effects has been approximately 5% units greater than the corresponding rates in placebo recipients. Discontinuation of the treatment because of side effects has been very rare. Serious skin reactions, including Stevens-Johnson syndrome and erythema multiforme have been reported rarely. Additionally, there are rare reports of hepatobiliary system disorders including hepatitis and elevated liver enzymes in patients with influenza-like illness.

There are no adequate data from the use of oseltamivir in pregnant women. In pre-licensing animal studies, no evidence of foetal toxicity or teratogenicity was observed. In rodents, oseltamivir has been shown to be secreted into milk. There is no information on secretion into breast milk in humans.

According to the approved product information in the European Union oseltamivir should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the foetus. Furthermore, oseltamivir should be used during lactation only if the potential benefit for the mother justifies the potential risk for the nursing infant.

Quality aspects related to pandemic use

Two dosage forms are commercialized:

- capsules 75 mg oseltamivir with a shelf life of 5 years.
- powder for reconstitution : 12 mg/ml oseltamivir with a shelf-life of 24 months, reconstituted solution: 10 days stored at 2 to 8 °C.

A magistral formulation is proposed for oseltamivir (API system).

The proposed magistral formulation consists of an oral solution containing 19.70 mg/ml of bulk oseltamivir phosphate (API; Tamiflu® grade) (corresponding to 15.0 mg/ml base), 1 mg/ml sodium benzoate (EP* or food grade) and water (EP* purified or potable water can be used). Sodium benzoate was chosen as antimicrobial

preservative as it dissolves rapidly in water, is well tolerated, is well established for oral solutions and is also as food grade readily available.

The method of preparation is well described and rather simple and can be prepared either in a pharmacy, in a hospital or in a suitable laboratory. There are no formal specifications (acceptance criteria + test methods) proposed by the MAH as the necessary equipment for quality control is not necessarily available in a hospital or in a pharmacy. This can be accepted in a pandemic situation as no quality control is performed in pharmacies when preparing other magistral preparations. The manufacturer will not supply the dosing device. Thus, no data on accuracy were presented. Member states will have to make sure that an adequate device is put at the disposal of the user/patient (part of stockpiling).

Data are presented to demonstrate the efficacy of the antimicrobial preservative sodium benzoate. The MAH does not test according to the European Pharmacopoeia standard test but according to a published low level challenge test using the same strains that are recommended European Pharmacopoeia. The method proposed by the company to test the efficacy of the preservative is acceptable as it simulates more the in-use conditions than the EP* test. The provided results demonstrate acceptable microbiological stability. The chemical / physical stability has been studied in the magistral preparation stored at 5 °C and 25 °C in colourless glass bottles, PET bottles and HDPE bottles. The following use up conditions were proposed and are supported by data:

- 3 weeks if stored not above 25 °C
- 6 weeks if stored at 5 °C

The MAH has prepared a guide (API User Manual) on how to prepare the magistral solution for the oseltamivir phosphate. The API user manual is comprehensive and very helpful in preparing the magistral solution. It has some advantages compared to the commercialised capsules formulation: cost, a shorter manufacturing cycle, availability, administration to children, even if from a logistic point of view the capsules are easier to dispense to the patient. However, if the API model is chosen, the procedures for preparing the solution and dispensing it to users/patients have to be organised carefully.

* Refers to European Pharmacopoeia.

The capsule model has a longer shelf life than the powder for reconstitution formulation but probably shorter than the bulk substance intended for the magistral formulation. In contrast to the magistral formulation, the use of capsules is supported by the full regulatory package and extensive clinical experience. The logistics of distribution are less complicated when commercial packages are used.

However, its use will be more expensive and the rate of production (to obtain sufficient stocks) is slower. Capsules are not suitable for use by small children.

Regulatory status

Medicinal products containing oseltamivir (Tamiflu®) have been approved centrally within the European Union by the European Commission. Please see the European Public Assessment Report (EPAR) at <http://www.emea.eu.int>

Zanamivir

Clinical uses

Zanamivir is indicated for treatment of influenza A and B in adults and adolescents aged >12 years at a dose of 10 mg twice daily for five days. Zanamivir is not yet approved for prophylaxis in the EU.

Pharmacology

Zanamivir is another selective inhibitor of influenza neuraminidase (NA), the influenza virus surface glycoprotein enzyme. In principle, the presumed mechanism of action is the same as for oseltamivir (see above). The activity of the drug is a result of the replacement of a hydroxyl group at the C-4 atom by a guanidine group. The interaction of the guanidino group with two framework residues Glu 119 and Glu 227 results in tight affinity of zanamivir for the active site of the enzyme.

The oral bioavailability of zanamivir is low (2%, range 1–5%). Therefore, it is administered topically to airways using a specifically designed breath-activated device for inhaling powder, Diskhaler. The two major sites of deposition immediately following dosing were the oropharynx and the lungs (mean 77.6% and 13.2%, respectively). Thereafter, the inhaled zanamivir was rapidly eliminated via the oesophagus to the stomach and the intestines. The estimated zanamivir concentration in this area would be at least 1868ng/mL, which is approximately 1400 times the neuraminidase IC50. In the worst case

scenario, there should still be approximately 140 times the neuraminidase IC₅₀ at the peripheral lung. Measurable zanamivir levels have been demonstrated in nasal cavity after oral inhalation. The observed levels were in excess of the median zanamivir neuraminidase IC₅₀ of 0.9ng/mL for at least 12h post-dose.

The systemic exposure to zanamivir is low, less than 30% of the administered dose. It is not metabolised but is primarily excreted unchanged via the kidneys. Thus, renal or hepatic dysfunction will not influence the dosing. The dose does not need to be modified in the elderly or in children.

Zanamivir is not protein bound and not metabolised or modified in the liver. Clinically significant drug interactions are unlikely. Zanamivir, when given for 28 days, does not impair the immune response to the conventional influenza vaccine. The effect on live influenza vaccination is unknown.

The safe use of zanamivir in pregnancy has not been established. In rats and rabbits, zanamivir has been shown to cross the placenta. High doses of zanamivir were not associated with significant malformations in the rat and rabbit. Zanamivir should not be used in pregnancy unless the expected benefit to the mother is thought to outweigh any possible risk to the foetus. In rats, zanamivir has shown to be secreted into milk. There is no information on secretion into breast milk in humans. The use of zanamivir is not recommended in mothers who are breast feeding.

Efficacy data

• Treatment

The results of the pivotal phase III studies, all double-blind and placebo-controlled, demonstrated that inhaled zanamivir, at a dose of 10mg twice daily for 5 days, was efficacious in the treatment of influenza A and B, reducing the median time to alleviation of symptoms by 1.5 days. The duration of viral shedding is also shortened. The studies mostly enrolled younger, otherwise healthy subjects but high-risk subjects were also included. A shortening (1.5 days) of the time to alleviation of the disease was observed in a study of patients with respiratory disease. The treatment effect has been demonstrated in patients in whom the treatment was initiated within 48 hours after the onset of clinical symptoms. In a combined analysis of four phase III

trials, complications were significantly reduced from 29% of placebo patients to 22% of zanamivir patients. Use of antibiotics for treatment of complications was reduced from 19% of placebo to 14% of zanamivir patients. The use of zanamivir is not expected to impair the effect of conventional influenza vaccines.

• Prophylaxis

Zanamivir is approved in 19 markets for prophylaxis at a dose of 10 mg once daily during the period of exposure risk.

Studies have been conducted in a number of different settings, including communities, nursing homes and households. In the phase III studies, subjects received study medication for 10 (household prophylaxis) – 28 days (community prophylaxis), depending of the type of prophylaxis. The efficacy in the community prophylaxis studies ranged between 60% and 83%. The efficacy in the postexposure prophylaxis in households was 79-81%. Studies in nursing homes suggested a protective efficacy of 29%–56%.

Sensitivity of influenza strains to zanamivir

In vitro: 50% inhibition at 0.64nM–7.9nM against influenza A and B. Within the frame of the NA inhibitor susceptibility network (NISN) over 1000 of clinical influenza isolates recovered from 1996 to 1999 have been tested and the mean zanamivir IC₅₀s were 0.76, 1.82 and 2.28 for the subtypes H1N1, H3N2 and influenza B, respectively. There was no evidence of naturally occurring resistance to zanamivir in any of the isolates. Further 2691 isolates have been tested during the post-approval period (see below).

It is suggested that NA inhibitors would be effective against the 1918 pandemic virus. Investigators have generated recombinant influenza viruses possessing the 1918 HA, NA and M segments. The other pandemic strains H2N2 (1957), H3N2 (1968), and H1N1 (1977) were also inhibited in both tissue culture and in mice by zanamivir.

In vitro studies have demonstrated that zanamivir is able to inhibit the different neuraminidase subtypes. The inhibitory profile was somewhat different from the profile of oseltamivir. Data from animal models suggest that zanamivir is effective against the A/Hong Kong/156/97 (H5N1) virus that caused fatal illness in Hong Kong in 1997. Intranasally administered zanamivir protects mice against lethal challenge with A/HK/156/97 (H5N1)

influenza virus, reducing viral replication in the lungs (by approximately 2 log₁₀) and reducing morbidity and mortality compared with untreated mice.

Other studies showed that zanamivir partially protects chickens from A/chick/Victoria/1/85 (H7N7), but failed to protect chickens against other highly virulent viruses of NA subtypes N1, N2, N3, N7, N8, although there is *in vitro* activity against the neuraminidase enzyme for these sub-types. This discrepancy may be due the fact that some influenza strains are able to replicate outside the respiratory tract where zanamivir is not available. However, studies in a mouse model using avian H5N1, H6N1 and H9N2 strains showed that intranasal zanamivir significantly reduced viral titres in the lungs and completely blocked the spread of virus to the brain, with the conclusion that systemic spread may be related to the level of virus replication in the lungs.

Mechanisms of viral resistance

In vitro studies have shown that mutations in both the haemagglutinin and neuraminidase are associated with resistance development over prolonged passage. Resistance mutations in the NA result in reduced affinity of NA for the inhibitor. Resistance mediated by HA mutations has been attributed to reductions in the affinity of HA for the sialylated glycoconjugates, thereby reducing the dependence of viral replication on NA activity. The clinical significance of HA mutations is unknown. Interestingly, some strains that are resistant to oseltamivir have retained sensitivity to zanamivir.

Clinical significance and surveillance systems of viral resistance

A global neuraminidase inhibitor susceptibility network (NISN) has monitored susceptibility of influenza isolates circulating world wide before the introduction of the neuraminidases (1997-1999) and following approval. The susceptibility of 2691 isolates from 1999–2002, post-licensure of the neuraminidases, was monitored and only three isolates (0.1%) had resistance-associated mutations. The clinical use of zanamivir is still relatively limited but, for the time being, zanamivir-resistant viruses have not been isolated from immunocompetent individuals who have received zanamivir.

Adverse effect profile and contraindications

The only contraindication is hypersensitivity to the product. Zanamivir was well tolerated in the adult/adolescent treatment studies. The most commonly reported AEs were typical of the signs

and symptoms of influenza and occurred with similar frequency in the zanamivir and placebo groups. However, inhalation of the zanamivir has been rarely associated with bronchospasm that may be severe in patients with bronchial asthma and chronic obstructive pulmonary disease.

Quality aspects related to pandemic use

Relenza Rotadisk® 5 mg is registered via the Mutual Recognition procedure in the old member states and via national procedures in the new member states. There is no difference in the Diskhale® and Rotadisk® blister packs supplied to the EU and non EU-market. The key specifications for release and end of life are very similar for most markets.

Shelf-life: 3 years (stored at < 30 °C) but may be extended to 5 years.

According to the marketing authorization holder, the manufacturing capacity has been created to meet demand of expected pandemic stockpiling. In case of a pandemic situation (import of non EU stock), it may be possible to return the stock to a registered packaging site in the EU for repackaging and release of the packs. A batch specific variation is to be submitted and approved by the relevant authority to allow importation and immediate use of the packs.

Due to the formulation (powder for inhalation) and the need for a device, there is no magistral formulation available.

Regulatory status

Medicinal products containing zanamivir (Relenza®) have been approved via the Mutual Recognition Procedure within the European Union.

Goals of antiviral use during influenza pandemics

Influenza antiviral medicinal products and pandemic influenza vaccines have a complementary role in the management of an influenza pandemic. In contrast to pandemic vaccines, influenza antivirals can be used from the very early phase of the influenza pandemic.

The estimates of efficacy of the influenza antivirals in a pandemic situation are largely based on their use in treatment and prophylaxis of seasonal influenza epidemics. However, the epidemiological pattern, the disease severity and demographics of patients of the pandemic influenza

Properties of influenza antiviral medicinal products

Property	Amantadine	Oseltamivir	Zanamivir
Mode of action	M2 ion channels blockade	Neuraminidase inhibition	Neuraminidase inhibition
Adverse effects	CNS effects, nausea, vomiting, palpitation Rare. Cardiac arrhythmias, seizures	Common: Nausea, vomiting, headache Rare to very rare: hypersensitivity; skin reactions; hepatitis, elevated liver enzymes	Very rare: bronchospasm
Warnings (some variation at the member state level)	Prostatic hypertrophy Narrow angle glaucoma Agitation and confusion History of seizure, psychosis or delirium Severe hepatic or renal dysfunction	Hypersensitivity reactions	Bronchospasm
Use during pregnancy	Not recommended	Only if the risk of infection exceeds the risk to the foetus	Only if the risk of infection exceeds the risk to the foetus
Use in children	Very limited data	Used in children from one year of age Not recommended for children < 12 Mo	Limited data on children Not suitable for children <5 years
Contraindications (variation at EU member state level)	Hypersensitivity to the product. Severe renal failure; History of convulsions; History of gastric ulcerations; Severe heart disease	Hypersensitivity to the product Use in children under one year of age not recommended	Hypersensitivity to the product
Drug-drug interactions	Anticholinergic agents Several medicinal products affecting CNS Combination diuretics Quinine, quinidine	Not known	Not known
Effect: treatment prophylaxis	Modest Good initially, may be lost due to resistance	Modest Good	Modest Good
Route of administration	Oral	Oral	Inhalation with a device
Site of action	Systemic	Systemic	Respiratory tract
Effect on past pandemic strains	Yes (in vitro and in vivo)	Yes (in vitro)	Yes (in vitro)
Effect on H5N1 "bird flu" strains	Questionable	Yes (in vitro, experimental in vivo); Probably clinically	Yes (in vitro, experimentally in vivo)
Resistance	Common in treatment	Rare (except in treatment of children)	Rare
Formulations	Tablets	Capsules, powder for solution, a magistral formulation (oral solution)	Powder for inhalation

may be different. These differences may have implications for the optimal posology of the antivirals. Nevertheless, the goals for the use of antivirals and vaccines should be the reduction of morbidity and mortality due to the influenza infection.

The usefulness of antivirals for treatment of influenza is restricted by the need to initiate treatment within two days of the onset of clinical symptoms. Even then, the treatment effect is modest and uncertain against the pandemic strains. Early treatment of a large number of patients in a pandemic situation requires a well functioning distribution system.

Thus, successful use of antivirals during a pandemic cannot be based on treatment of symptomatic disease alone because of their limited efficacy, risk of viral resistance and the availability of the products (stocks and logistics of early treatment). Based on currently available clinical data and on results of modelling studies, it appears that targeted prophylaxis of influenza will be a feasible approach to the use of influenza antivirals during an influenza pandemic:

- For certain groups of individuals who are essential for the key functions of the society (e.g. health care workers, decision makers, police, firemen etc.), long-term prophylaxis should be considered in the very early phase of the pandemic and until a vaccine becomes available.

- For the general population, prompt treatment of index cases combined with prophylactic use by their close contacts (post-exposure prophylaxis) is a useful approach to mitigate the effects of the pandemic and to slow down the progression of the pandemic at the time when an effective vaccine is not available. In certain circumstance of the early phase of the pandemic, containment of the disease may be possible.

A wider long-term prophylactic use of antivirals will have a major impact on the size of the necessary stocks as well as on the distribution system. The feasibility of this approach remains uncertain. Factors which might be taken into account in the choice of antiviral product(s) may be based on the pharmacological properties of the available agents, possibilities to use them in different groups of individuals, as well as on practical aspects related to the stockpiling and distribution. In spite of the uncertainty, the recommendation takes notice of the current epidemiological situation, i.e. the widespread infection of domestic and wild animals by the H5N1 strain of influenza virus ("bird flu") – a potential ancestor of a pandemic.

Safety and Efficacy Issues

Safety challenges of preventing malaria during pregnancy:

Malaria is a significant cause of mortality and morbidity among pregnant women in malaria endemic countries including Ghana where it accounts for nearly 10% of all deaths in pregnancy. It is also associated with anaemia and low birth weight infants. As part of the programme to roll back malaria, Ghana has embarked upon a comprehensive policy change revising the recommendations for malaria prophylaxis in pregnancy and replacing chloroquine with amodiaquine+artesunate as first line treatment for uncomplicated malaria in adults and children. In the previous policy, pregnant women received 300 mg chloroquine base (two tablets) weekly for the duration of pregnancy. In addition to the long period of prophylaxis, the bitter taste of chloroquine and its mild but sometimes irritating side effects, such as intense itching, led to poor compliance. In fact, one audit at a teaching hospital in the country indicated very poor adherence to this recommendation by prescribers and patients alike. Unsurprisingly, little progress was made in the fight against malaria in pregnancy.

Under Ghana's new malaria policy, prophylaxis of malaria in pregnancy involves intermittent preventive treatment (IPT) whereby pregnant women receive three courses of sulphadoxine-pyrimethamine (SP) at a minimum of four weekly intervals provided the first course is given after 16 weeks and the final course is administered before 36 weeks. Each course consists of three tablets of SP (500 mg+25 mg) administered under direct observation by a health worker. IPT with SP is associated with high levels of compliance and has been shown in several studies to reduce malaria-associated morbidity and mortality in pregnancy, with a huge reduction in low birth weight infants. In Ghana, SP is contraindicated in women with glucose-6-phosphate dehydrogenase (G6PD) deficiency though the policy change requires no a priori testing for G6PD deficiency. The contraindi-

cation in G6PD deficiency is due to the serious haematological and dermatological events that sometimes occur in G6PD-deficiency patients who take sulpha-containing medicines. With an estimated prevalence of G6PD deficiency of between 20–30% and with most of the population not knowing their G6PD status, the new policy presents challenges.

The Ghana National Centre for Pharmacovigilance in collaboration with the National Malaria Control Programme and with funding from the Global Fund developed a simplified pharmacovigilance system for SP in IPT. This involved development of a very simple tick-box *SP Adverse Event Form* which was incorporated into the antenatal records of each pregnant woman in 20 pilot districts. Health workers were trained on the use of the forms which may be filled if any adverse event occurs during the 30-minute observation period after administration of SP. At every subsequent ante-natal clinic visit, questions on possible adverse events which might have occurred following administration of the previous dose of SP are solicited and a form filled if necessary. In addition, community based agents who are non-formal carers living in the community and supervising nominated pregnant women were also trained on filling the forms and a tabulation of adverse events reported included in the monthly returns they make. Linking adverse events reported to their monthly returns (which also includes the number of insecticide treated nets supplied) ensures that issues of safety are constantly kept in mind.

After nearly 24 months of careful roll out, the safety of SP for IPT in pregnant Ghanaian women appears assured. More than 55 000 women have received the first, second or third courses of SP for IPT with fewer than 100 adverse events reported. The level of reporting is admittedly low but the intense engagement between the National Pharmacovigilance Centre and the various districts involving once weekly calls to enquire about adverse events means that any reported cases of serious adverse events will be reported immediately. In fact, the first case of a faxed "spontaneous" report at the National Centre for Pharmacovigilance was received when a women

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on SP for IPT was hospitalized with mucocutaneous reactions. The woman in question recovered without sequelae and was told to avoid SP. She has since given birth successfully with no obvious congenital problems in the child. Reports have also been sent by courier and mail to the National Centre or the National Malaria Control Programme indicating the seriousness attached to safety monitoring by the pilot districts. In one district, an increased reporting of unspecified symptoms after changes in suppliers of SP raised the possibility of a pharmaceutical defect and this was subsequently confirmed: a simplified pharmacovigilance system in a resource-limited environment has averted a potential catastrophe!

The use of SP for IPT in Ghana is being extended nationwide to all 138 administrative districts. This will raise logistical problems for the national pharmacovigilance centre which has to develop ways of engaging all districts regularly whilst encouraging improved reporting. However, by building on and utilizing the existing health care system and allowing reporting through the known primary health care centres, polyclinics, district and regional hospitals, it is likely that reporting rates will be reasonable. This campaign, like the national pharmacovigilance programme, is being supported by a strong media programme involving regular national TV and radio programmes and occasional newspaper articles all focusing on safety. A majority of the population rely on the radio for health information, and promoting drug safety monitoring through the radio seems to work very well.

Malaria in pregnancy can be prevented with medicines, and evidence obtained so far from Ghana shows that the use of SP for IPT even in this country of high G6PD deficiency is safe. Continuous intensive monitoring is however advocated to obtain more data on the safety of SP in IPT and also because intense monitoring may lead to quicker identification of drug quality problems. This pharmacovigilance system is relatively inexpensive and can be replicated in several resource-constrained environments regardless of the level of training of the formal and non-formal healthcare personnel involved.

WHO International Drug Monitoring Programme: 28th meeting

The Twenty-eighth Annual Meeting of Representatives of National Centres participating in the WHO Programme for International Drug Monitor-

ing was held from 26 to 29 September 2005 in Geneva, Switzerland. The meeting focused on several key issues in pharmacovigilance:

- How pharmacovigilance centres react to high profile withdrawals.
- Pharmacovigilance in public health programmes.
- Reporting adverse events following immunization (AEFI).
- Developing an international taxonomy for patient safety events.
- Reporting and learning from patient safety events.
- The relevance of the International Classification of Diseases (ICD) in pharmacovigilance.

Improving effectiveness of response to high profile withdrawals

Regulatory authorities have responsibility for undertaking several procedures prior to withdrawing a medicine from the market, including a review of available data and assessing the risk/benefit. They must also communicate such risks to prescribers in an adequate manner and identify alternative product options. However, depending on the capacity of the agency, there is divergence among regulatory agencies in carrying out these procedures. Well-resourced, and well-established regulatory bodies are generally able to analyse company trial data, local adverse drug reactions (ADR), data from the WHO ADR database and medical literature. Countries with less-developed regulatory systems may have resource and/or capacity constraints, limiting them to reviewing local data. Although trials may be ongoing in their country they may not have access to the company trial data and will have to rely on communications from regulatory authorities in other countries on action taken. In general, from a regulator's perspective, access to drug safety information can often be compromised by inappropriate timelines for reporting, confidentiality requirements, media and government pressure, and gaps in human resources and skills. Inadequate information hampers appropriate and timely regulatory measures, which in turn can erode professional and public confidence.

Collective action proposed for improving international regulatory efficiency includes:

- improving information-sharing and multilateral collaboration;

- strengthening regulatory capacity by releasing ADR reports with any evaluations or risk-communication material in or under development in a timely fashion;
- promoting electronic exchange and discussion on safety issues of global concern; and
- undertaking literature review of high risk products and creating a data bank for such literature.

Pharmacovigilance in public health programmes

There are compelling reasons for including pharmacovigilance in public health programmes particularly those designed to treat HIV/AIDS, malaria, tuberculosis and helminth infections. Introduction of new drugs is often based on efficacy trials of limited duration, providing little knowledge of long-term safety. Available data on drug toxicity are obtained mainly from industrialized countries, but medicines may have a different clinical and operational context in developing countries or be used in combinations not assessed in developed countries. Life threatening side effects, co-morbidities and co-treatments impact on selection of preferential and alternative drugs

At present, few if any public health programmes include a pharmacovigilance component in their design. In several countries that run public health programmes, there are no pharmacovigilance centres and hence there are no systematic methods for collecting ADR reports in these countries. In those countries where both systems exist, they often function in parallel, with little communication between the national pharmacovigilance centres and the public health programmes.

Participants at the meeting urged public health programmes to build pharmacovigilance into their agendas. As a first step, the concepts in the ICH E2E guideline on Pharmacovigilance Planning can be used to develop a system for meeting the needs of specific infectious diseases and drug treatment related safety concerns in public health programmes. This guideline describes a method for summarizing identified risks of a drug, potential risks, missing information, and at-risk populations and situations where the product is likely to be used. It proposes a model structure for a pharmacovigilance plan and sets out principles of good practice for the design and conduct of observational studies.

A spontaneous reporting system would be useful for flagging initial concerns before verification using targeted active-surveillance programmes. These may be further reinforced with randomized clinical trials.

Vaccines: How to improve reporting to WHO

There are many barriers to reporting adverse events following immunization (AEFI). There is a need to address data ownership, lack of communication between immunization programmes and pharmacovigilance centres; differing objectives, lack of education on the importance and benefits of AEFI reporting, insufficient AEFI-oriented elements in current pharmacovigilance training programmes, taxonomy and definitions of adverse events/reactions. In addition, an insufficient number of vaccine centres participate in national centres meetings.

In order to improve this situation, work should begin on improving political will and commitment, communication, media, visibility, education and training, terminology, and development of a common reporting system.

Reference: Feature. *WHO Pharmaceuticals Newsletter*, No. 4, 2005. <http://www.who.int/medicines>

Statins and memory loss

Canada — The role of HMG-CoA reductase inhibitors, or statins, in cardiovascular protection is well established. However, evidence in the current literature is conflicting as to the effect of statins on cognitive function (1). It has been postulated that statins may prevent dementia of the Alzheimer type through inhibition of beta-amyloid formation and thus decreased production of neurofibrillary tangles and plaques (2). Other studies have suggested that statins can contribute to memory loss (1–4). The proposed mechanism relates to cholesterol's essential role in myelin production. Statins, especially the more lipophilic ones (e.g., atorvastatin and simvastatin), may cross the blood-brain barrier and decrease the amount of central nervous system (CNS) cholesterol necessary for the formation of myelin (2, 3). Inadequate myelin production may result in demyelination of nerve fibres in the CNS and thus lead to memory loss (2). Memory impairment is listed in the product monograph for pravastatin (Pravachol®) (5).

From the date of marketing of statins in Canada to May 2005, Health Canada received 19 reports of amnesia suspected of being associated with these drugs (Table 1). The onset was reported to occur within 1 month after starting statin therapy in 5 cases, within 1 year in 7 cases and after 1 year in 3 cases. Four cases did not report an onset date. Eleven reports described that the amnesia resolved or improved when the drug was discontinued or the dose reduced, and one of them also described a positive rechallenge. Other reports did not provide this information.

Given these findings, changes in cognitive status temporally associated with statin therapy should be monitored (2).

Extracted from: Canadian Adverse Reaction Newsletter, Volume 15, Issue 4, October 2005.

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New safety information on long-acting beta-2 agonists

Canada — Health Canada has advised of a possible increased risk of asthma-related deaths associated with long-acting beta-2 agonists.

The medications involved are salmeterol, (Serevent®), formoterol, (Foradil® and Oxeze®); as well as two combination products containing salmeterol or formoterol in addition to an inhaled corticosteroid. The combination product with salmeterol is sold as AdvairR®, while the formoterol product is sold as Symbicort®. Long-acting beta-2 agonists are prescribed as regular treatment to prevent asthma symptoms such as wheezing, shortness of breath and cough.

This advisory is based on a Health Canada analysis of findings from an asthma research trial

Table 1: Reports submitted to Health Canada of amnesia* suspected of being associated with statins from date marketed in Canada to 31 May 2005†

Variable	Atorvastatin	Cerivastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
Date marketed	1997	1998‡	1994	1988	1990	2003	1990
Total no. of AR reports with amnesia	8	1	0	2	0	4	4
Positive dechallenge§	4	1	-	2	-	2	1
Median age (and range) of patients, yr	70 (50-78)¶	NR	-	61 (41-81)	-	57 (51-69)	67 (65-81)¶

Note: AR = adverse reaction, NR = not reported.

**Includes forgetfulness, memory disturbance, memory impairment and memory loss according to the World Health Organization Adverse Reaction Terminology (WHOART).*

†These data cannot be used to determine the incidence of ARs or to make quantitative drug safety comparisons between the products because ARs are underreported and neither patient exposure nor the amount of time the drug was on the market has been taken into consideration.

‡Cerivastatin withdrawn from the market in 2001.

§Response to withdrawal of the drug.

¶Age unknown in 1 case.

known as the Salmeterol Multi-center Asthma Research Trial, or SMART. The SMART study began in 1996 at the request of the US Food and Drug Administration (FDA), due to increasing safety concerns about regular long-term use of salmeterol in the treatment of asthma. The study of approximately 30 000 patients was prematurely halted in January 2003 after an interim analysis suggested an increased risk of asthma-related death in patients who use salmeterol (as compared to a placebo) in addition to their usual asthma therapy. The SMART study data was reviewed by an FDA advisory committee in July 2005 that looked at the safety of these asthma medications. The committee voted unanimously to keep this class of drugs on the market.

Although not conclusive, the SMART study suggests that risks may be higher in African-American patients and in those patients who were not being treated with inhaled corticosteroids at the start of the study.

Health Canada recommends that:

- Salmeterol and formoterol can only be used with an appropriate dose of inhaled corticosteroid as determined by a physician.
- Long-acting beta-2 agonists are not a substitute for inhaled or oral corticosteroids.
- Serevent®, Foradil® or Advair® should never be used to treat acute or sudden onset of asthma symptoms and attacks.
- Symbicort® is not indicated for the treatment of sudden asthma symptoms and attacks.
- Oxeze® may be used to treat acute, or the sudden onset of asthma symptoms, in patients 12 years and older.
- Medical attention should be sought if a patient's use of asthma medications becomes less effective, or if more inhalations than usual are required.
- Patients must not stop or reduce their asthma therapy without first consulting their prescribing physician. Abruptly stopping medications may result in deteriorating asthma control, which can be life-threatening.

The prescribing information for Serevent® and Advair® has been updated. Health Canada is

engaged in an ongoing review of these products, and is in the process of reviewing the safety data for the other long-acting beta₂ agonists. Further action may be taken if necessary.

Reference: *Health Canada Advisory*, 2005-107. 4 October 2005

Meningococcal vaccine and Guillain Barre syndrome

United States of America — The Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC) are alerting consumers and health care providers to five reports of Guillain Barre syndrome (GBS) following administration of meningococcal conjugate vaccine A, C, Y, and W135 (Menactra®), manufactured by Sanofi Pasteur. It is not yet known whether these cases were caused by the vaccine or are coincidental.

Guillain Barre Syndrome (GBS) is a serious neurological disorder that can occur, often in healthy individuals, either spontaneously or after certain infections. GBS typically causes increasing weakness in the legs and arms that can be severe and require hospitalization.

Meningococcal infection is a major cause of bacterial meningitis, affecting approximately 1 in 100 000 people annually. The infection can be life threatening: 10–14 percent of cases are fatal and 11–19 percent of survivors may have permanent disability.

At the present time there are no changes in recommendations for vaccination; individuals should continue to follow doctors' recommendations. FDA and CDC are not able to determine if any or all of the cases were due to vaccination. The current information is very preliminary and the two agencies are continuing to evaluate the situation.

Because of the potentially serious nature of this matter, FDA and CDC are asking any persons with knowledge of any possible cases of GBS occurring after Menactra® to report them to the Vaccine Adverse Event Reporting System (VAERS) to help the agencies further evaluate the matter. Individuals can report to VAERS on the web at www.vaers.hhs.gov and <http://www.vaers.hhs.gov>

Reference: *FDA News*, P05-66. 30 September 2005.

Trastuzumab and possible cardiotoxicity

United States of America — The manufacturer of trastuzumab (Herceptin®) has updated health care professionals on cardiotoxicity information obtained from the National Surgical Adjuvant Breast and Bowel Project (NSABP) study (B-31), a randomized, Phase III trial that was conducted in 2043 women with operable, HER2 over-expressing breast cancer (IHC 3+ or FISH+). This study demonstrated a significant increase in cardiotoxicity in patients who were randomized to the trastuzumab-containing arm as compared to patients who received chemotherapy alone.

Trastuzumab as a single agent is indicated for the treatment of patients with metastatic breast cancer whose tumours overexpress the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease. Trastuzumab in combination with paclitaxel is indicated for treatment of patients with metastatic breast cancer whose tumours overexpress the HER2 protein and who have not received chemotherapy for their metastatic disease. Trastuzumab should be used in patients whose tumours have been evaluated with an assay validated to predict HER2 protein overexpression. It should be noted that trastuzumab is not indicated for any other patients, including those with newly diagnosed, operable breast cancer.

Risk factors for cardiac dysfunction will be analysed with data from both the NSABP B-31 and the North Central Cancer Treatment Group NCCTG N9831 trials, when available.

Reference: Extracted from information provided by Genentech, Inc., August 2005 <http://www.gene.com>

Trastuzumab: interim treatment recommendations

France — The French Medicines Agency (Afssaps) has advised health care professionals of new information concerning use of trastuzumab (Herceptin®) as adjuvant treatment in breast cancer associated with over-expression of the HER2 protein. The Agency's action follows preliminary results from three trials recently reported by the American Society of Clinical Oncology. In the group of women with this kind of breast cancer, overall survival was 8% with a 34% reduced risk of death, while recurrence was reduced by 46%. The National Cancer Institute

and AFSSAPS have drafted an interim guide for use of trastuzumab as adjuvant treatment in breast cancer.

The decision to initiate treatment must be made based on several criteria. Among these, trastuzumab should only be used in patients where the tumour over-expresses HER2. This should be determined by validated laboratory diagnosis.

Because of known cardiotoxicity and risk of cardiac failure, the risk benefit should be carefully assessed against known cardiac infection together with regular cardiac monitoring every three months during treatment and thereafter six months, one year and five years following suspension of treatment.

Reference: Information and treatment guide is available at <http://www.afssaps.sante.fr>.

Oseltamivir paediatric adverse events

United States of America — At its meeting on 18 November 2005, the Pediatric Advisory Committee (PAC) will review the safety report for oseltamivir (Tamiflu®). The review will include adverse event reports, a literature review, and analysis of clinical trial data. A CDC presentation will provide background information on the United States Surveillance Data on Influenza and their new paediatric influenza surveillance efforts.

The review of adverse event reports will discuss paediatric deaths, serious skin reactions, and neuropsychiatric events. These events have been reported almost entirely in children from Japan, where a number of adverse event reports were identified possibly associated with the use of oseltamivir in children 16 years of age or younger. These reports were primarily related to unusual neurologic or psychiatric events such as delirium, hallucinations, confusion, abnormal behaviour, convulsions, and encephalitis.

These events were reported almost entirely in children who received oseltamivir according to Japanese treatment guidelines (very similar but not identical to US treatment guidelines). The review identified a total of 12 deaths in paediatric patients since approval, all in Japanese children. In many of these cases, a relationship to oseltamivir was difficult to assess because of the use of other medications, presence of other

medical conditions, and/or lack of adequate detail in the reports.

The review also identified severe skin reactions in some pediatric patients. These events were not all reported in Japanese children and have also been reported in adults. Severe skin reactions in all age groups are currently being reviewed in more detail.

Initially, it was not clear why the neuropsychiatric adverse events and deaths were reported almost entirely in Japanese children. The FDA receives adverse event reports from all over the world and usually adverse events are roughly the same from different reporting countries. The reports of death and neuropsychiatric events associated with oseltamivir, almost entirely from Japan, was unusual enough to prompt further evaluation.

The FDA requested additional information from both the pharmaceutical company which produces Tamiflu®, and the Japanese Ministry of Health, Labor, and Welfare. FDA then evaluated several possible explanations for the neuropsychiatric adverse events.

Review of the available information on the safety of oseltamivir in paediatric patients suggests that the increased reports of neuropsychiatric events in Japanese children are most likely related to an increased awareness of influenza-associated encephalopathy, increased access to oseltamivir in that population, and a coincident period of intensive monitoring adverse events.

Reference: Food and Drug Administration. Information Page. Questions and Answers. [http://www.fda.gov/cder/durg/infopage/tamiflu/November 17, 2005](http://www.fda.gov/cder/durg/infopage/tamiflu/November%2017,%202005)

Duloxetine hydrochloride and hepatic effects

United States of America — The manufacturer of duloxetine hydrochloride (Cymbalta®) has informed health care professionals of new safety information regarding hepatic injury (including hepatitis and cholestatic jaundice) obtained from postmarketing reports.

Some of these reports indicate that patients with preexisting liver disease who take duloxetine may have an increased risk for further liver damage. The new labelling extends the precaution in patients with substantial alcohol use to include those patients with chronic liver disease.

Postmarketing reports have described cases of hepatitis with abdominal pain, hepatomegaly and elevation of transaminase levels to more than twenty times the upper limit of normal with or without jaundice, reflecting a mixed or hepatocellular pattern of liver injury. Cases of cholestatic jaundice with minimal elevation of transaminase levels have also been reported. The combination of transaminase elevations and elevated bilirubin, without evidence of obstruction, is generally recognized as an important predictor of severe liver injury. Postmarketing reports also indicate that elevated transaminases, bilirubin and alkaline phosphatase have occurred in patients with chronic liver disease or cirrhosis. Because it is possible that duloxetine and alcohol may interact to cause liver injury or that duloxetine may aggravate pre-existing liver disease, duloxetine should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

Reference: Communication from eli Lilly of 5 October 2005 posted at <http://www.fda.gov/>

Intrathecal baclofen: incidents with implantable drug pump system

Canada — Baclofen (Lioresal®) is a muscle relaxant and antispastic agent (1). Intrathecal baclofen (ITB) is indicated for the management of severe spasticity in patients with spinal cord injury or multiple sclerosis unresponsive to oral baclofen therapy or who experience unacceptable adverse reactions at effective oral doses. It is also used in patients with spasticity of cerebral origin (1). ITB injection, which delivers the drug directly to its site of action, can achieve cerebrospinal fluid levels up to 30 times higher than those achieved using oral baclofen therapy, with minimal serum concentrations (2). Patients receive baclofen as a continuous intrathecal infusion from a surgically implanted pump system (1). During chronic therapy, most patients require gradual dose increases because of decreased responsiveness or disease progression.

From 1992 to June 2005, Health Canada received 21 reports of adverse reactions suspected of being associated with ITB. Ten reports implicated the implantable drug pump system (IDPS). Of these 10 reports, 5 involved problems specific to the catheter system and 5 involved coma following implantation surgery (suspected improper pump preparation leading to inadvertent bolus). Device-related adverse events are mentioned in

the Lioresal® Intrathecal product monograph (1) and in the Medtronic pump systems information (3).

One of these reports has already been published in the medical literature and describes a case with confusing symptomatology (4). A 6-year-old boy with cerebral palsy underwent implantation of an intrathecal baclofen pump to manage his spasticity. Two years later, he was admitted to hospital twice in a 3-day span with symptoms of apparent baclofen overdose. His parents described a 2-month history consistent with intermittent symptoms of baclofen overdose in the morning (reduced consciousness, hypotonia) followed by symptoms of baclofen tolerance or withdrawal later in the day (increased rigidity). Routine investigation of the IDPS did not yield any significant findings, but a microfracture of the catheter was visible on electron microscopy. The catheter was replaced, the patient recovered, and a lower maintenance dose was established. In this case, the intermittent symptomatology was thought to have been due to posture-related effects on the catheter microfracture. It was postulated that the microfracture was closed when the patient was supine at night and forced open when he was positioned upright during the day, leading to leakage of the medication (4).

The exact nature of catheter-related complications associated with the use of IDPS may not always be identified using the various procedural checks in an established protocol (5). In some cases, surgery fails to identify the cause of the catheter malfunction; however, replacement of the catheter may restore the clinical response to ITB (5).

Health care professionals should be aware of potential IDPS-related adverse events, which may present with confusing signs and symptoms. Device-related issues should be considered when evaluating the need for dose adjustments.

Extracted from: Canadian Adverse Reaction Newsletter; Volume 15, Issue 4, October 2005.

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Ibritumomab tiuxetan therapeutic regimen: cutaneous reactions

United States of America —The manufacturer of ibritumomab tiuxetan (Zevalin®) has advised health care professionals of new safety information involving severe cutaneous or mucocutaneous reactions, some with fatal outcome, which have been reported during post-marketing experience. Similar events have been associated with rituximab (Rituxan®), a component of the Zevalin® therapeutic regimen. The potential risk of these reactions should be considered and patients experiencing a severe cutaneous or mucocutaneous reaction should not receive any further components.

The warning information has been revised to include erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous dermatitis, and exfoliative dermatitis in patients who received the therapeutic regimen. Some of these events were fatal. The onset of reactions was variable; in some cases, acute, (days) and in others, delayed (3-4 months).

Reference: Information communicated by Biogen October 2005 at <http://www.biogenidec.com>

Interactions with implantable medical devices

Canada/France — Patients with active implantable medical devices and systems (AIMDS) are at risk of injury from interactions between the AIMDS and other medical devices used for diagnostic or therapeutic purposes. Such interactions could damage some AIMDS resulting in loss of therapy from these units, and could cause tissue damage resulting in severe injury or death. Patients may be at risk even if the leads are not connected to an implantable device or even if the device is off.

On 2 April 2003, Health Canada issued a notice warning of the risks of tissue overheating, serious injury and death in this group of patients when subject to shortwave (radiofrequency) or microwave diathermy therapy. Since then, Health Canada has become aware of further international reports of serious injury resulting from interactions between AIMDS and other medical devices (2).

In 2003, the French Health Products Safety Agency, Agence française de Sécurité sanitaire des Produits de Santé (AFSSAPS), assembled a working group to analyse the recommendations of AIMDS manufacturers and make recommendations to health care professionals who perform certain diagnostic and therapeutic procedures on patients with AIMDS. The recommendations of the group were released by AFSSAPS in February 2005 (3).

The risk of interactions between AIMDS and other medical devices used for diagnostic or therapeutic purposes depends on many parameters.

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Liquid chemical polymer and serious adverse events

United States of America — The manufacturer of Enteryx® Procedure Kits and Enteryx® Injector Single Packs has informed health care professionals of serious adverse events, including death, occurring in patients treated for gastro-oesophageal reflux disease (GERD). Physicians should stop injecting Enteryx® immediately.

Enteryx® is a liquid chemical polymer which is intended to be injected into the lower oesophageal sphincter. The device polymerizes into a spongy material shortly after injection and once injected cannot be removed.

The serious adverse events involve unrecognized transmural injections into structures surrounding the oesophagus. Transmural injections can potentially result in death or serious injury. Signs and symptoms of transmural injection can include: chest pain, flu-like symptoms, pneumonia, atelectasis, reactive pneumonitis, mediastinitis, pneumo-mediastinum, reactive pleuritis, pleural effusion, pericardial effusion, syncopal episodes, and flank pain. Some cases of transmural injection were not recognized at the time of the procedure or during immediate follow-up; these occurred even though fluoroscopy was used throughout the procedure. When injected into the aorta, Enteryx® may migrate to and occlude blood vessels which supply other organs including the kidneys.

The Food and Drug Administration is aware of other injuries not caused by user technique or transmural injection. Recent literature cites two cases in which serious mediastinal events suggestive of possible inflammatory reactions occurred even though proper procedure was followed. Other adverse events not associated with transmural injection have also been reported to the FDA, some of them presenting 4 to 7 weeks after injection. They include dysphagia from oesophageal stenosis or stricture that required dilation procedures, and weight loss. These later-onset events appear to be different from the immediate onset, short-lived events observed during the approval trial.

Reference: *FDA Preliminary Public Health Notification.* Recall of Boston Scientific ENTERYX® Procedure Kits and ENTERYX® Injector Single Packs for Treatment of Gastro-oesophageal Reflux Disease (GERD). 14 October 2005 and <http://www.fda.gov/cdrh/medicaldevicesafety/atp/101405-enteryx.html>.

Atomoxetine and suicidal thinking in children and adolescents

United States of America — the Food and Drug Administration (FDA) has directed the manufacturer of atomoxetine (Strattera®) approved for the treatment of attention deficit hyperactivity disorder (ADHD) in paediatric and adult patients, to revise the labelling to include warning statements of an increased risk of suicidal thinking in children and

adolescents. A Patient Medication Guide (MedGuide) should also be distributed to patients when Strattera® is dispensed.

The increased risk of suicidal thinking for this drug was identified in a combined analysis of 12 short-term (6–18 weeks) placebo-controlled trials. The trials involved a total of over 2200 patients and showed a greater risk of suicidal thinking during the first few months of treatment.

A similar analysis in adult patients treated with Strattera® for either ADHD or major depressive disorder (MDD) found no increased risk of suicidal ideation or behaviour.

Reference: *FDA Public health advisory and FDA News*, P05/65. 29 September 2005.

Paroxetine: first trimester exposure and congenital malformations

Canada — The manufacturer of paroxetine (Paxil®) has informed health care professionals of important new safety information regarding use during the first trimester of pregnancy.

The preliminary report of a retrospective epidemiological study of 3581 pregnant women exposed to paroxetine or other antidepressants during the first trimester indicates an increased risk for paroxetine compared to other antidepressants.

Cardiovascular malformations with ventricular septal defects were the most frequent type of cardiovascular defect reported in the paroxetine-exposed group. Other independent studies of pregnancy outcome following first trimester exposure to antidepressants, including paroxetine, provide conflicting evidence regarding rate of birth defects.

As currently stated in the Product Monographs, paroxetine should be used during pregnancy only if the potential benefit justifies the potential risks to the fetus. Prescribers should carefully evaluate

this new information when considering the use of paroxetine in women who are pregnant or planning pregnancy. This information should be discussed with the patient.

The manufacturer has posted the results of the study on its Clinical Trial Website at <http://ctr.gsk.co.uk/welcome.asp>.

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Spontaneous monitoring systems are useful in detecting signals of relatively rare, serious and 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.

Access to Medicines

Canada and the “Jean Chrétien Pledge to Africa”

On 30 August 2003, negotiations among World Trade Organization (WTO) Members resulted in a landmark decision (the “Decision”) waiving two compulsory licensing provisions (Articles 31[f] and [h]) of the WTO Agreement on Trade-Related Intellectual Property Rights (the “TRIPS Agreement”), which were thought to be a barrier to effective responses to public health problems. In doing so, WTO members with pharmaceutical manufacturing capacity could establish compulsory licensing regimes authorizing persons, other than the patent holder, to manufacture a lower-cost version of a patented pharmaceutical product for export to an eligible importing Member. Consequently, developing and least-developed countries with insufficient or no manufacturing capacities for pharmaceutical products could benefit from greater access to needed medicines.

In September 2003, Canada became the first WTO member and G-8 country to announce its intention to implement the Decision domestically. Implementation of the Decision was accomplished on 14 May 2004 with the passage of *An Act to amend the Patent Act and the Food and Drugs Act — The Jean Chrétien Pledge to Africa* (JCPA) (S.C.2004, c.23). This provided a coming into force of the legislation upon adoption of regulatory provisions. The regulations were adopted on 14 May 2005 and are referred to as the *Use of Patented Products for International Humanitarian Purposes Regulations* (S.O.R./2005-141). This legislative framework, which amended both the Canadian *Patent Act* and the *Food and Drugs Act*, was introduced to ensure timely access to affordable versions of patented pharmaceutical products urgently needed by least-developed or developing countries to fight HIV/AIDS, malaria, tuberculosis and other epidemics. Although not required by the Decision, Canada introduced changes to the *Food and Drugs Act* and its regulations to ensure that pharmaceutical products exported under the JCPA regime meet

Canadian standards for safety, quality and efficacy.

The following is a summary of the process to be followed by importing countries and pharmaceutical manufacturers who wish to avail themselves of Canada’s JCPA regime. A chart outlining the major required steps is also found at the end of this article.

Eligible importers

Although the Decision is an agreement between WTO Member Countries, Canada has, for humanitarian reasons, opted to implement it in a manner that enables both WTO and non-WTO Member Countries to import urgently needed pharmaceutical products (drugs and medical devices) under compulsory licence. Schedules 2, 3 and 4 of Canada’s *Patent Act* list the countries eligible to make use of the regime. While non-WTO least-developed countries are automatically eligible to import under the Canadian regime, non-WTO developing countries may do so upon request and on the condition that they be eligible for official development assistance according to the Organization for Economic Cooperation and Development (OECD).

In order for an eligible importing country to access the Canadian regime, it must publicly disclose the name and quantity of the product it is seeking, and, if that product is protected by a domestic patent, indicate that it has or will be issuing a compulsory licence authorizing imports of the product. Unless the importer is a least-developed country, notice of the above information must also contain a declaration that it has no or insufficient domestic capacity to manufacture the required product. More highly developed countries, which are listed on Schedule 4, must also indicate that they require the patented product to respond to a public health emergency. WTO Member Countries must provide notice of the above information to the WTO, copies of which will be posted on the WTO’s Website (http://www.wto.org/english/tratop_e/trips_e/public_health_e.htm). All other countries must provide notice to the Government of Canada, through diplomatic channels, copies of which will be posted on a Website maintained by Canada’s Minister of Foreign Affairs.

Article prepared by Doug Clark, Industry Canada; Amanda Collier and Catherine Lemay, Health Canada.

Nongovernmental organizations may also act as purchasers of licensed pharmaceutical products under Canada's regime, with the permission of the importing country's government.

Eligible pharmaceutical products

Products eligible for export under Canada's regime are listed in Schedule 1 to the *Patent Act*. The initial list in Schedule 1 was composed primarily of products on the World Health Organization Model List of Essential Medicines that are listed on the Patent Register in Canada (<http://www.patentregister.ca>). The Schedule will be amended from time to time to ensure that the list of eligible products remains current with the public health needs of developing countries. To facilitate this process, the *Patent Act* provides for the creation of an expert committee to advise the Government of Canada on the need to add products to the list. Schedule 1 was recently amended for the first time by the addition of a fixed-dose combination of three antiretroviral drugs used in the treatment of HIV/AIDS.

Although not required by the Decision, all pharmaceutical products to be exported under Canada's regime must meet the same safety, efficacy and quality standards as those destined for domestic consumption. A special review stream has been established by Canada's Minister of Health in order to expedite the authorization of such products. Applicable fees normally associated with the regulatory review process will be remitted to the sponsor by Health Canada upon meeting certain criteria, such as proof of a valid compulsory licence and having filed a claim for remission within 45 days of licence issuance by the Commissioner of Patents.

Application process

A Canadian pharmaceutical manufacturer that has entered into a contract with an eligible importing country for the supply of an eligible pharmaceutical product must file an application for a compulsory licence with the Canadian Intellectual Property Office's Commissioner of Patents (the "Commissioner"). The application must identify, *inter alia*, the pharmaceutical product for which a licence is sought, the patent(s) which protect(s) it, the quantity to be manufactured, the country to which it is to be exported and the identity of the purchaser. The Canadian Intellectual Property Office has waived the fees normally associated with a licence application.

In keeping with Article 31(b) of TRIPS, the application must also include a declaration that the applicant had, at least 30 days prior to applying for the compulsory licence, unsuccessfully sought a voluntary licence from the patentee and, in doing so, provided the latter with information that is substantially the same as the information appearing in the application. In the case of a WTO Member, this declaration must be accompanied by a copy of that country's notification to the WTO of its intention to import the product to which the application relates. In the case of a non-WTO Member Country, this must be accompanied by a copy of the country's notice to the Government of Canada of its intention to import that product. In either case, the applicant must also provide the Commissioner with a declaration setting out the patent status of the product in the importing country.

The manner in which the above information is communicated to the Commissioner is prescribed by Canada's *Use of Patented Products for International Humanitarian Purposes Regulations*. Form 1 of these regulations sets out the information that must appear in the application itself. Form 2 sets out the information that must appear in the applicant's declaration that a voluntary licence was unsuccessfully sought from the patentee. Forms 3 to 7 set out the information that must appear in the applicant's declaration as to the identity of the pharmaceutical product and its patent status in the importing country (whichever of Forms 3 to 7 applies in the circumstances will depend on whether the importing country is a WTO or non-WTO Member and on the patent status of the product in that country).

If the application:

- meets the content requirements described above;
- specifies an eligible product on Schedule 1, which the Minister of Health has notified is compliant with the *Food and Drugs Act* and its regulations as being safe, efficacious, of good quality, and distinctive from the innovative version of the product sold in Canada; and,
- names a country on Schedules 2, 3 or 4,

then the Commissioner is required to grant the applicant a compulsory licence to manufacture and export the product in question. The actual

content of the licence issued by the Commissioner is set out in Form 9 of the above-named regulations. Within 15 days of the day on which the authorization was granted; or, the day on which the supply agreement to which the licence relates was entered into, the licensee must submit Form 8 and a copy of the supply agreement with the importing country to the Commissioner and the patentee(s).

Anti-diversion measures

Before the Commissioner may issue a compulsory licence, notification must be received from the Minister of Health that the product meets the requirements of the *Food and Drugs Act* and its regulations. In addition to meeting all of the rigorous regulatory requirements for safety, efficacy and quality as domestic products, these products must also have specific markings, colouring and labelling to be distinguishable from the patented versions available on the Canadian market. This is designed to minimize the risks of re-importation into Canada or diversion to other countries.

All product labels and all solid dosage form products, such as tablets and capsules, must have the letters "XCL" permanently displayed. For solid dosage forms, the colour must be significantly different from the version sold in Canada. All labels, samples of which must be provided to the Minister of Health, must bear the export tracking number issued by the Minister of Health, as well as the prescribed phrase "For export under the General Council Decision. Not for sale in Canada." Pre-export inspections will be performed to verify the distinguishing features on these products and labels.

Before a pharmaceutical product subject to a licence may be exported, the licence holder must also establish a website setting out information about the name of the licenced product, its distinguishing characteristics, the identity of the importing country, the amount to be manufactured and sold for export, as well as information identifying every known party who will be handling the product while it is in transit from Canada to the importing country.

Lastly, the licence holder must provide, within 15 days before the product is exported, a notice specifying the quantity to be exported, as well as every known party that will be handling the product while it is in transit. This notice must be provided to the patent holder(s), the importing country named in the application and the person or entity that has purchased the product.

Renewal

The term of a compulsory licence is 2 years from its date of issuance. A licence may be renewed once for an additional 2 years, if an application for renewal (Form 10) is filed prior to expiry of its initial term. The actual content of the renewed licence issued by the Commissioner is set out in Form 11 of the above named regulations.

Royalties

Paragraph 3 of the Decision calls for "adequate remuneration" to be paid to the patentee on a case-by-case basis, taking into account the economic value to the importing country of the use that has been authorized by the exporting country. Under Canada's regime, the royalty rate is calculated by multiplying the monetary value of the supply agreement between the licence holder and the importing country by an amount which fluctuates on the basis of that country's standing on the United Nations Human Development Index (UNHDI).

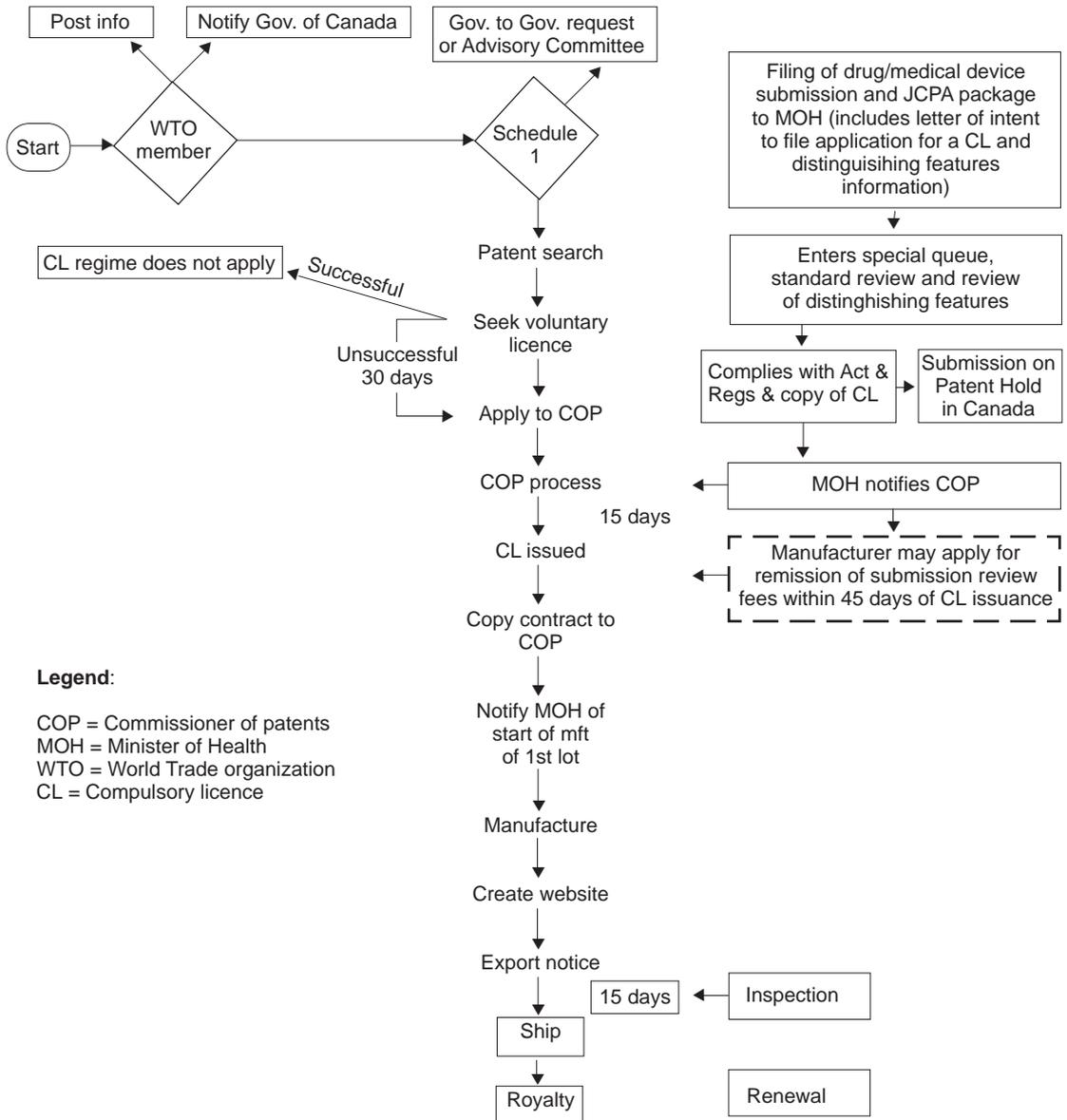
The formula to determine the royalty rate is: 1, plus the number of countries on the UNHDI, minus the importing country's rank on the UNHDI, divided by the number of countries on the UNHDI, multiplied by 0.04. For example, in 2004 Nigeria was ranked number 151 of the 177 countries listed on the UNHDI. Therefore, the royalty rate that would be applicable to exports of pharmaceutical products to Nigeria would be $[(1+177-151)/177] \times 0.04 = 0.0061$ or 0.61 percent.

Where the importing country is not listed on the UNHDI, the royalty rate is to be calculated by substituting the individual country's rank in the formula with the average rank of all countries appearing on the same schedule. However, an exception to this rule has been made in the case of non-WTO Member developing countries that are unranked. Although these countries are individually eligible for listing on Schedule 4, their individual rank in the formula will be replaced by the average rank of all countries appearing on Schedule 3, as the latter is thought to better reflect the level of development of the countries in question.

Good faith clause

The Decision was adopted by the General Council in light of the General Council Chairperson's Statement stipulating that this Decision must be used in good faith in order to deal with public health problems and not for commercial policy objectives. A provision in Canada's *Patent Act*, which has come to be known as the "good

Use of Patented Products for International Humanitarian Purposes: application process



faith clause", gives effect to Canada's obligation to implement the Decision in keeping with the Chairperson's statement, by providing patent holders with the right to challenge an export licence in court where there is good cause to believe it is predominantly commercial, as opposed to humanitarian, in nature.

In order to bring such a challenge, the patent holder must first establish that the average price of the licenced product is 25% or more of the average price of the equivalent patented product in Canada. If this test is met, the court will look to the other merits of the application and determine, based on a number of statutory considerations, whether the licence is commercial in nature. An absolute defence exists to any such challenge if the licence holder can establish that the product's average price remains less than its direct supply cost plus 15%.

If the court determines that the agreement is commercial in nature, it may make an order, on any terms that it considers appropriate, either terminating the licence or requiring the licence holder to pay, in addition to the royalty otherwise required to be paid, an amount that the court considers adequate to compensate the patent holder for the commercial use of its patent.

Termination by federal court

Finally, the court may also make an order terminating an export licence where the patent holder can establish that one of the following events has transpired:

- the application for the licence contained materially inaccurate information;

- the licence holder has failed to establish a website;
- the licence holder has failed to provide an export notice;
- the licence holder has failed to pay the prescribed royalties;
- the licence holder has failed to provide a copy of its supply agreement ;
- the product has been re-exported in a manner contrary to the Decision;
- the product has been exported in a quantity greater than the quantity authorized to be manufactured under the licence;
- where the importing country is a non-WTO Member, that country has failed to adhere to the principles underlying the Decision.

Legislation and regulations

1. Canada's enabling legislation, *An Act to amend the Patent Act and the Food and Drugs Act (The Jean Chrétien Pledge to Africa)* may be obtained electronically at http://www.parl.gc.ca/PDF/37/3/parlbus/chambus/house/bills/government/C-9_4.

2. Accompanying Regulations at <http://canadagazette.gc.ca/partII/2005/20050601/pdf/g2-13911.pdf>

3. Additional information on how to apply for a compulsory license in Canada may be found at http://strategis.ic.gc.ca/sc_mrksv/cipo/jcpa/p3-e.html

Regulatory Action and News

Safety update on paediatric use of oseltamivir

European Union — A potential influenza pandemic remains currently of high public interest and the European Medicines Agency (EMA) has provided a safety update on oseltamivir (Tamiflu®) see page 274).

Oseltamivir is an antiviral approved in the European Union for the treatment of influenza in children between 1 and 13 years of age and for the prevention and treatment of influenza in adolescents over 13 years and adults.

Two cases of alleged 'suicide' associated with treatment of influenza (involving a 17-year-old boy in February 2004 and a 14-year-old boy in February 2005) were reported to the EMA. In both cases the adolescents exhibited abnormal/disturbed behaviour, which led to their deaths. So far, no causal relationship has been identified between the use of Tamiflu® and psychiatric symptoms (such as hallucination and abnormal behaviour). The EMA stresses that the assessment of psychiatric events during Tamiflu® treatment is difficult because:

- Other medicines are often taken at the same time as Tamiflu®;
- Patients with influenza and a high fever can show psychiatric symptoms. This is particularly relevant for children and elderly patients.

All adverse reactions are monitored and assessed by the Agency's scientific committee, the Committee for Medicinal Products for Human Use (CHMP) on a continuous basis. At its meeting of 14–17 November 2005, the CHMP decided to request the marketing authorization holder of Tamiflu® to provide a cumulative safety review of all available data on serious psychiatric disorders, including all case reports with a fatal outcome where Tamiflu® was involved. EMA will make a statement on the outcome of this evaluation.

Reference: EMA Press release. EMA/385013/2005. <http://www.emea.eu.int>.

Influenza virus composition for 2006 southern hemisphere winter

World Health Organization — It is recommended that vaccines to be used in the 2006 season (southern hemisphere winter) contain the following:

- an A/New Caledonia/20/99(H1N1)-like virus;
- an A/California/7/2004(H3N2)-like virus. (The currently used vaccine virus is A/New York/55/2004);
- a B/Malaysia/2506/2004-like virus

National control authorities should approve the specific vaccine viruses used in each country. National public health authorities are responsible for making recommendations regarding the use of the vaccine.

Circulating influenza viruses in humans are subject to permanent antigenic changes which require annual adaptation of the influenza vaccine formulation. Updates in influenza vaccine composition should ensure the closest possible match between the influenza vaccine strains and the circulating influenza strains; ensuring this match is one of the foundations for influenza vaccine efficacy.

Reference: *Weekly Epidemiological Record*, **80**: 346 (2005).

International biosafety guidelines for influenza vaccine production

World Health Organization — The WHO Expert Committee on Biological Standardization met in Geneva from 24–28 October 2005. One of the new guidelines that was established describes international biosafety expectations for both pilot-scale and large-scale vaccine production of human influenza vaccines produced in response to a pandemic threat, and the quality control of these vaccines.

Tests required to evaluate the safety of candidate influenza vaccine reference viruses prior to

release to vaccine manufacturers are also specified in the document, which is thus relevant to both development and production activities, and also to vaccine and biosafety regulators. A detailed risk assessment is presented. This concludes that the likelihood of direct harm to human health if non-reassortant wild-type H5 or H7 viruses with multiple basic amino acids at the HA cleavage site and high in vivo pathogenicity are used for vaccine production, would potentially be high. Such viruses also pose a high risk to animal public health.

Stringent vaccine biosafety control measures, defined as BSL3 enhanced (pandemic influenza vaccine) are defined to manage the risk from vaccine production and quality control using such viruses in the pre-pandemic period. For all other vaccine strains, for example reassortants derived from H5 or H7 strains in which the multiple basic amino acid HA0 cleavage site has been removed, the direct risk to human health is very remote.

Nevertheless, there is an indirect risk to human health since there is a theoretical possibility of secondary reassortment with normal influenza human viruses and that such reassortant viruses may be replication-competent in humans, whilst having avian-like coat proteins. Although very unlikely, the secondary reassortant could become adapted to human infection and transmission which, if vaccine production was taking place in the pre-pandemic period, would have serious public health consequences.

The biosafety control measures that are proposed, defined as BSL2 enhanced (pandemic influenza vaccine), take this, and also potential risks to animal health, into account. Facility and personal protection specifications are provided for both BSL2 enhanced and BSL3 enhanced biosafety levels and guidance is provided on biosafety management and implementation within a vaccine production facility. Tests to be performed on candidate vaccine reference strains prior to release to vaccine developers depend on the type of virus but include, at a minimum, ferrets (or other susceptible mammals) and also, where necessary, chickens, egg embryos, plaque assays and sequencing.

Reference: World Health Organization. *Biosafety guidelines for the production and quality control of human influenza pandemic vaccine strains*. <http://www.who.int/biologicals>

Veralipride: withdrawal following review of risk/benefit

Spain — The Spanish Agency for Medicines and Health Products has announced the marketing withdrawal of the menopausal treatment veralipride (Agreal®), an antidopamine agent marketed in Spain since 1983 for the treatment of hot flushes and other menopausal symptoms.

The Spanish Pharmacovigilance System (SEFV) has received various reports of suspected adverse reactions including depression, anxiety, and neurological complaints including dyskinesia and Parkinsonism, some of which have been severe. Neurological reactions have been linked to treatment, while the psychological states have been linked to treatment withdrawal on finalization of the treatment course or interruption of treatment.

The Committee on Safety of Human Medicines (CSMH) has therefore reviewed the information available and carried out a risk/benefit assessment, which they consider unfavourable.

In consequence, the Agency has suspended marketing of veralipride (Agreal®) as of 15 June 2005.

Reference: Communication from Agencia Española de Medicamentos y Productos Sanitarios.. <http://www.agemed.es>

Pemoline: liver Injury risk and market withdrawal

United States of America — The Food and Drug Administration (FDA) has concluded that the overall risk of liver toxicity from Cylert® and generic pemoline products outweighs the benefits of this drug. In May 2005, the manufacturer of Cylert® chose to stop sales and marketing in USA. All generic companies have also agreed to stop sales and marketing of pemoline tablets and chewable tablets. Pemoline is a central nervous system stimulant indicated for the treatment of attention deficit hyperactivity disorder (ADHD).

This product was considered second line therapy because of its association with life threatening hepatic failure (http://www.fda.gov/cder/foi/label/2003/016832s022_017703s018lbl.pdf). FDA was aware of 13 reports of liver failure resulting in liver

transplant or death, usually within four weeks of onset of signs and symptoms of liver failure. Although the absolute number of reported cases of liver failure with pemoline is not large, the reporting rate for liver failure with pemoline is 10 to 25 times greater than the background rate of liver failure in the general population.

Cylert® will remain available through pharmacies and wholesalers until supplies are exhausted; no additional product will be available.

Reference: <http://www.fda.gov/medwatch/report/hcp.htm>

Nelarabine approved for leukaemia and lymphoma

United States of America — The Food and Drug Administration (FDA) has announced the approval of nelarabine (Arranon®) for marketing in the United States under the Orphan Drug and Accelerated Approval Program. This is a new drug to treat adults and children with T-cell acute lymphoblastic leukaemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL), whose disease has not responded to or has relapsed following at least two chemotherapy regimens. Arranon is the first drug to treat this limited population of patients.

Nelarabine is a cancer chemotherapy drug that kills cancer cells by blocking the cell's ability to reproduce. Rapidly dividing cancer cells are more sensitive to cancer chemotherapy drugs than are more slowly dividing normal cells. The evidence to support approval consisted of complete disappearance of cancer cells in some patients, although in most cases the cancer later returned. In those patients who responded, the disappearance of cancer cells was sometimes accompanied by return of normal blood cell counts.

Acute lymphoblastic leukaemia (ALL) is an aggressive disease that progresses rapidly without effective therapy. Each year, an estimated 2400 children and 1200 adults are diagnosed with ALL in USA. Common side effects reported with nelarabine treatment are fatigue, nausea, vomiting and diarrhoea.

Reference: *FDA News*, P05-79. 31 October 2005.

EMA proposes new, faster scientific advice procedure

European Union — The European Medicines Agency (EMA) has launched a two-month public consultation exercise on proposed improvements to the way it provides scientific advice on the research and development of new medicines. The provision of scientific advice to sponsors, whether pharmaceutical industry or other researchers, is one of the main priorities for EMA and is a key part of the Agency's response to the EU strategy for improving the competitiveness of European-based research and development of medicines.

The main features of the revised procedure include the earlier and greater involvement of external experts in developing advice, and a faster delivery of the advice to sponsors.

Reference: European Medicines Agency, EMA/311762/2005. London, 22 September 2005. <http://www.emea.eu.int>

Withdrawal of Infanrix HepB®

European Union — On 25 April 2005 the European Commission adopted a decision withdrawing the marketing authorization for the medicinal product for human use "Infanrix HepB". It followed the notification by the marketing authorisation holder (MAH) to voluntarily withdraw Infanrix HepB for marketing reasons. The MAH confirmed that this decision was based on commercial reasons and not due to any safety related concerns.

Infanrix HepB®, [diphtheria toxoid, tetanus toxoid, acellular pertussis components, recombinant hepatitis B surface antigen (r-HBsAg)], was indicated for active immunization of all infants from the age of 2 months against diphtheria, tetanus, pertussis and hepatitis B. It should be noted that there are other valid European Union marketing authorizations which contain the same antigens.

Reference: European Medicines Agency Public Statement. London 4 August 2005. EMA/245029/2005. <http://www.emea.eu.int>

Precautionary suspension of Hexavac®: lowered immunogenicity

Switzerland — Swissmedic has advised health care professionals of suspension of the marketing authorization for Hexavac®.

Hexavac® is a combined paediatric vaccine offering protection against diphtheria, tetanus, pertussis, poliomyelitis, *Haemophilus influenzae* and hepatitis B. It has been available in Switzerland since 2001 for use in infants at 2, 4 and 6 months with a follow up dose at 15–24 months.

The European Medicines Agency (EMA) and Swissmedic have identified lowered immunogenicity of the hepatitis B component, probably due to variability in the manufacturing process. This effect is accentuated when combined with the 5 other components of Hexavac®. This may lead to insufficient protection in the long term.

Reference: Swissmedic suspend l'autorisation de mise sur le marché du vaccin Hexavac®. Swissmedic Journal 9/2005.lite et Hemophilus

Environmental risk assessment for human and veterinary medicinal products

European Union — The European Medicines Agency held a conference with interested parties on 27–28 October 2005 to discuss the current state and future developments in the area of environmental risk assessment for human and veterinary medicinal products.

Medicinal products used for the treatment of humans or animals may have an impact on the environment. The new EU pharmaceutical legislation requires companies to submit an environmental risk assessment as part of a marketing authorization application.

More than 130 participants from the Agency's Committee for Medicinal Products for Human Use (CHMP) and Committee for Medicinal Products for Veterinary Use (CVMP), the Committees' Working Parties, national competent authorities, the European Commission, academia, dedicated interest groups and industry met in four sessions to review and discuss key issues on:

- Exposure of the environment to veterinary and human medicinal products.

- Regulatory aspects of environmental risk assessment for medicines.
- Risk management and mitigation measures.
- Future developments and impact.

Exposure of the environment to veterinary and human medicinal products

The subject of pharmaceuticals in the environment has become more important to regulators and industry as a consequence of the widespread detection of pharmaceuticals in environmental samples. Exposure-modelling and results of monitoring studies were discussed, and data gaps required for modelling and priority-setting were flagged. The environmental concentrations observed are unlikely to exert acute ecotoxicological effects. However, there is a need to obtain more data on the chronic ecotoxicological effects of human pharmaceuticals before potential risks can be ruled out. Different models currently used in EMA and VICH guidelines, comparisons with actual exposure data, and proposals for improvements to exposure-modelling, that should be representative throughout Europe, were presented and discussed.

Environmental risk assessment and the regulatory aspects for pharmaceuticals

For human and veterinary medicinal products, the legal requirements of the new legislation for an environmental risk assessment (ERA) have been clarified. ERA applies to all new applications, to variations (Type II) and to line extensions. In relation to renewals for veterinary medicinal products, the consideration of the risks to the environment is required as part of the risk-benefit re-evaluation. However, the potential impact on the environment is not part of the assessment of the risk-benefit balance of a human medicine. If appropriate, measures, to limit the impact on the environment shall be envisaged on a case-by-case basis.

A new technical guidance document on environmental impact assessment of veterinary medicines, supplementing the current VICH guidelines with technical details, is currently being prepared and should be sent out for consultation soon. Following public consultation, there are no major concerns from industry on the current technical content of the draft ERA guideline on human medicinal products. Key discussion points were whether the predicted environmental concentra-

tion (PEC) estimation be based on default values or actual data, and the possibility of introducing more flexibility and science-driven testing strategy. Depending on the number of changes that are necessary, the finalisation of the guideline could be possible in early 2006.

Risk management/mitigation — Too much or not enough?

The speakers addressed the perspective of the national competent authorities on risk management/mitigation. A comparison was made between the risk management/litigation possibilities for veterinary and human medicinal products. Intensive discussion on the acceptability of labelling as an effective mitigation measure took place. Discussions on the appropriate way of addressing the ecotoxicity assessment for veterinary and human medicinal products that are already authorised took place, and the meeting was informed that the German Authorities have

launched a research project addressing this with respect to veterinary medicinal products, involving other EU Member State authorities.

Future developments and impact

ERAPharm is a promising project, funded by the European Commission, intended to improve both the environmental hazard and exposure-assessment for pharmaceuticals. The project will finish in September 2007. In addition, the Water Framework Directive under preparation by the European Commission was discussed, which shall merge different pieces of legislation addressing chemicals in the aquatic environment in the near future. A prioritization list was developed for chemicals of concern, and, in the near future, pharmaceuticals might also be included.

Reference: European Medicines Agency, EMEA/359945/2005 0.10. <http://www.emea.eu.int>

Recent Publications, Information and Events

Promoting drug use in the community

The International Training course on Promoting Rational Drug Use in the Community is a groundbreaking 10-day course developed by WHO to respond to a clear need for more effective planning, research and implementation of rational medicine use practices in the community. It will be held at the Indian Institute of Health Management Research, Jaipur, India, 15–24 January 2006.

The course concentrates on methods to study and remedy inappropriate medicine use in the community. Participants will be exposed to practical approaches to investigating and prioritizing medicine use problems, and how to develop effective strategies for change. There will be a focus on rational use of antibiotics, drug use in AIDS, Malaria and TB.

The course is participatory in nature and uses the knowledge, skills and experience of participants as a major resource throughout. Teaching methods include group activities, fieldwork, presentations and discussions. The course will be conducted in English, and given its interactive nature, the participants are required to have a good command of this language to participate efficiently. The participants will be exposed to a wide range of national and international experience.

Reference: Information can be obtained from: jbpapna@iihmr.org; jsbpapna@gmail.com; prudc.india@gmail.com

Registration of fixed dose combinations

Fixed-dose combination (FDC) medicines are increasingly used in the treatment of a wide range of conditions and are particularly useful in the management of public health infections such as HIV, tuberculosis and malaria.

FDCs have advantages where treatment in a fixed ratio has been shown to be safe and effective for an identified patient population.

Additionally, where resources are limited, the cost of an FDC product and its administration may be less than that of separate products. Simpler logistics of distribution, improved patient compliance, and reduced resistance of antimicrobials are also potential advantages.

Guidelines for registration of fixed-dose combination medicinal products have now been published by WHO to provide advice for countries when developing regulatory requirements and for industry when proposing new products for marketing. The Guidelines include sections on quality and bioavailability, data requirements, preclinical pharmacology and safety, product information, summary of product characteristics, and postmarketing studies. Of particular interest is the concise information on paediatric dosage forms. Four appendixes are also provided and cover co-packaging, scientific literature acceptability, preformulation studies and clinical trial relevance.

World Health Organization. Specifications for Pharmaceutical Preparations. *Technical Report Series*, No. 929, 2005. Annex 5. Available from WHO at <http://www.who.int/medicines/> or publications@who.int

Sources and prices of HIV medicines and diagnostics

The World Health Organization has published the *2005 Sources and prices of selected medicines and diagnostics for people living with HIV/AIDS*. This report, on finished products of selected HIV-related medicines and diagnostics, includes over 90 active ingredients in 166 dosage forms, and 36 different HIV test kits. The report is issued annually, and is available as a printed document or downloadable from WHO, UNICEF, UNAIDS, and Médecins sans Frontières (MSF). This endeavour is closely linked with the prequalification project managed by WHO.

The June 2005 report includes updated prices of pharmaceutical products and diagnostic tests. Apart from antiretroviral medicines, it includes medicines used to treat a range of opportunistic infections, for pain relief, for use in palliative care,

for the treatment of AIDS-related cancers and for the management of drug dependence. It also provides information on a range of HIV/AIDS test kits for initial diagnosis of the infection, and on-going monitoring of antiretroviral treatment and drug resistance.

The report has also a section on registration status of products and information about registered products per country which is available on CD-ROM. The eighth edition of an MSF document, "Untangling the web of price reductions: a pricing guide for the purchase of ARVs for developing countries" is also included as part of the report and informs the reader about current discount prices offered by pharmaceutical companies.

Reference: *Sources and prices of selected medicines and diagnostics for people living with HIV/AIDS.* <http://www.who.int/eh/>

Screening guidelines for women exposed to DES in utero

Australia — New guidelines on Screening to Prevent Cervical Cancer: Guidelines for the Management of Asymptomatic Women with Screen Detected Abnormalities, was published on 9 June 2005. These guidelines contain a section concerning women exposed in utero to diethylstilboestrol (DES). The guidelines advise that women with DES exposure should be offered annual cytological screening and colposcopic examination of both the cervix and the vagina.

The Australian Adverse Drug Reactions Committee (ADRAC) has previously published information on the risks associated with DES exposure (1).

Reference:

1. ADRAC. The legacy of diethylstilboestrol (DES) from the 50s and 60s. *Aust Adv Drug Reactions Bull* 2004;**23**:10.
2. Extracted from: Australian Adverse Drug Reactions Bulletin, Volume 24, Number 5, October 2005
3. Guidelines for the Management of Asymptomatic Women with Screen Detected Abnormalities. <http://www.health.gov.au/nhmrc/publications/synopses/wh39syn.htm>

The Blue Guide on advertising

The new Blue Guide on Advertising and Promotion of Medicines in the UK has been launched on 7 November 2005. The guide explains the regulations and provides clarification on the Agency's interpretation.

Advertising, including that of medicines, is acceptable provided it is in line with legislation and agreed standards of good practice. Medicines cannot be treated as an ordinary general commodity. They have the potential for harmful as well as beneficial effects and can cause serious problems if not used safely. For this reason, there are specific regulations that strictly control the advertising and promotion of medicinal products in the UK. All advertising and promotion of medicines must be responsible and of the highest standard to ensure the safe use of medicines both in self-medication and where medical supervision is required.

In recent years great progress has been made in information and communications technology and this is a fast and constantly evolving medium which also has considerable impact on medicines advertising in general. All means and methods used in the promotional marketing of medicines are subject to the legislation controlling advertising. The regulations lay down the requirements and restrictions for advertising, aimed at prescribers, suppliers, or the public. Central to this is the principle that the Regulations prohibit advertising of prescription only medicines to the public. The control of medicines advertising in the UK is based on a long established system of self-regulation as permitted under European law covering medicines advertising.

During 2003, the MHRA reviewed all its internal procedures for regulation of medicines advertising to ensure that processes are robust and effective in protecting public health. The revised Blue Guide provides further clarification on many issues and is intended to reflect the changes that have occurred in legislation governing the advertising of medicines.

Reference: Blue Guide on Advertising and Promotion of Medicines in the UK. <http://www.tso.co.uk/bookshop>.

Chronic airways disease guide

Prevalence of chronic airways diseases such as asthma, chronic obstructive pulmonary disease (COPD) and allergic rhinitis are on the increase. There is a great need for more and better care of these diseases. Many guidelines are often complicated and recommend use of resources not available in all primary health care settings.

The International Primary Care Airways Group has recently published a Guide for primary care physicians which sets out to show how management and improved patient care can be achieved with limited resources. The document encourages physicians worldwide to select practical diagnostic and therapeutic measures appropriate to the setting. It is recommended that a critical analysis is made of the population under care, set against prevailing conditions. In this way, the most effective interventions can be assessed.

The handbook describes an approach to diagnosis through a set of newly developed questionnaires and aids, and organizes the process of managing chronic airways diseases into colour-coded tracks to assess severity and aid therapy selection. The complete differential diagnosis of chronic respiratory disease is extensive, and non-respiratory or other causes need to be excluded: symptoms may be similar to those of tuberculosis, HIV and fungal or parasitic infections. Many patients may consequently need to be referred to an allergist, pulmonologist or other specialist.

Reference: International Primary Care Airways Group. *Chronic airways diseases: A guide for primary care physicians*. January 2005. <http://www.ginasthma.org>

Priority medicines for Europe and the world

In a Europe which is expanding and playing a pivotal role in many global challenges, this report has been developed to identify pharmaceutical gaps undermining efforts to control those diseases of public health importance which have so far been ignored. From a public health perspective, pharmaceutical gaps can be identified where treatments do not exist for diseases of importance, either because of a lack of basic scientific knowledge or delivery, or market failure.

Recent reviews of the pharmaceutical industry situation in Europe suggest that Europe is lagging behind the USA in its ability to generate, organize and sustain pharmaceutical innovation. Meanwhile, demographic patterns, increase in chronic diseases, and existence of high burden diseases, such as diabetes, cancer, Alzheimer disease and osteoarthritis, requiring heavy investment in research, continue to shape future challenges.

Key conclusions of the report identify antibacterial resistance and pandemic influenza as major threats to global public health — areas which could particularly profit from European technology, expertise and innovation. The report also underscores the importance of policies on smoking, and the role of information technology in creating opportunities for research and development of new treatments.

Reference: World Health Organization. *Priority Medicines for Europe and the World*. WHO/EDM/PAR/2004.7 from edmdoccentre@who.int or <http://www.who.int/medicines>

International Pharmacopoeia

Monograph for oral powders

The International Pharmacopoeia is collaborating with manufacturers, independent analytical drug quality control laboratories, national and regional pharmacopoeial bodies, research, governments, and regulatory bodies to provide a general monograph for oral powders. A draft proposal is provided below for comment. The requirements of this monograph do not necessarily apply to powders to be used for the preparation of oral solutions or suspensions.

Definition. Oral powders are preparations consisting of solid, loose, dry particles of varying degrees of fineness. They contain one or more active ingredients, with or without excipients and, if necessary, authorized colouring matter and flavouring substances. They are generally administered in or with water or another suitable liquid. They may also be swallowed directly. They are presented as single-dose or multidose preparations.

Each dose of a single-dose powder is enclosed in an individual container, for example a packet, a sachet or a vial. Multidose oral powders require the provision of a measuring device capable of delivering the quantity prescribed.

Manufacture. The manufacturing process for oral powders should meet the requirements of Good Manufacturing Practice, especially with regard to cross-contamination.

In the manufacture of oral powders, measures are taken to ensure a suitable particle size with regard to the intended use.

In the manufacture, packaging, storage and distribution of oral powders, suitable measures are taken to ensure their microbial quality.

The following information is intended to provide very broad guidelines concerning the main steps to be followed during production, indicating those that are the most important.

Appropriate measures should be taken to counteract segregation of the components of the powder mixture. Segregation takes place whenever a free-flowing powder consisting of particles of a range of sizes is handled, including the mixing stage and emptying of the mixer container. The prime means to counteract segregation is to use components of approximately the same particle size. Because of the risk of segregation, oral powders containing a low proportion of the active ingredient, for example, less than 5% of total mass, should preferably be prepared as single-dose preparations.

The intended mass of one dose of an oral powder should be at least 500 mg to minimize the effect of loss of powder when taken from a single-dose container or to allow a proper dosing when using a measuring device.

In the production of oral powders, the components of the powder mixture are passed individually through a sieve to remove lumps and particle aggregates. The weighed masses of the sieved components, preferably of a uniform particle size, are then transferred to a mixer suitable for mixing free-flowing powders. The greatest risk of segregation of the powder mixture occurs when emptying the mixer container and when the powder mixture is dosed into single-dose containers or multidose

containers. The suitability of the mixing equipment and the dosing devices is documented by a validation procedure.

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 the manufacture of oral powders should include the dosing by mass of the powder in the containers.

Visual inspection. Inspect the powder, using at least 20 containers for single-dose preparations. Evidence of physical and/or chemical instability is demonstrated by noticeable changes in physical appearance, including texture [e.g. clumping] or colour.

Uniformity of content. See the general requirements 5.1* Uniformity of content of single-dose preparations. Single-dose oral powders with a content of active ingredient of less than 5 mg or less than 5% of the total mass comply with the test, unless otherwise specified in the individual monograph. If the preparation has more than one active ingredient, the requirement applies only to those active ingredients that fall into the above category. *[Note from the Secretariat: it is proposed to apply the limits as for capsules and suppositories.]*

Uniformity of mass. See the general requirements 5. 2* Uniformity of mass of single-dose preparations. Single-dose oral powders comply with the test. If the test for uniformity of content is prescribed for all active ingredients, the test for uniformity of mass is not required. *[Note from the Secretariat: it is proposed to apply the limits as for capsules.]*

Uniformity of mass of doses delivered by the measuring device. The measuring device provided with a multidose oral powder complies with the test. Weigh individually 20 doses taken at random from one or more multidose containers with the measuring device provided and determine the individual and average masses. Not more than two of the individual masses deviate by more than 10% from the average mass and none deviates by more than 20%.

Labelling. Every pharmaceutical preparation must comply with the labelling requirements established under Good Manufacturing Practice.

The label should include:

- (1) the name of the pharmaceutical product;
- (2) the name(s) of the active ingredients; w should be used wherever possible;
- (3) for single-dose preparations, the amount of the active ingredient(s) per container and for multidose preparations, the amount of active ingredient in a suitable quantity by weight;
- (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. If the preparation contains volatile or hygroscopic ingredients, the oral powder should be kept in a tightly closed container.

* Refers to *The International Pharmacopoeia*

Requirements for specific types of oral powder

Effervescent powders

Definition. Effervescent powders are presented as single-dose or multidose preparations and generally contain acid substances and carbonates or hydrogen carbonates which react rapidly in the presence of water to release carbon dioxide. They are intended to be dissolved or dispersed in water before administration.

Storage. Effervescent powders should be kept in tightly closed containers.

Launch of new medicines website

Based largely on the results of a recently conducted user survey, the World Health Organization has developed a new medicines website at <http://www.who.int/medicines/>

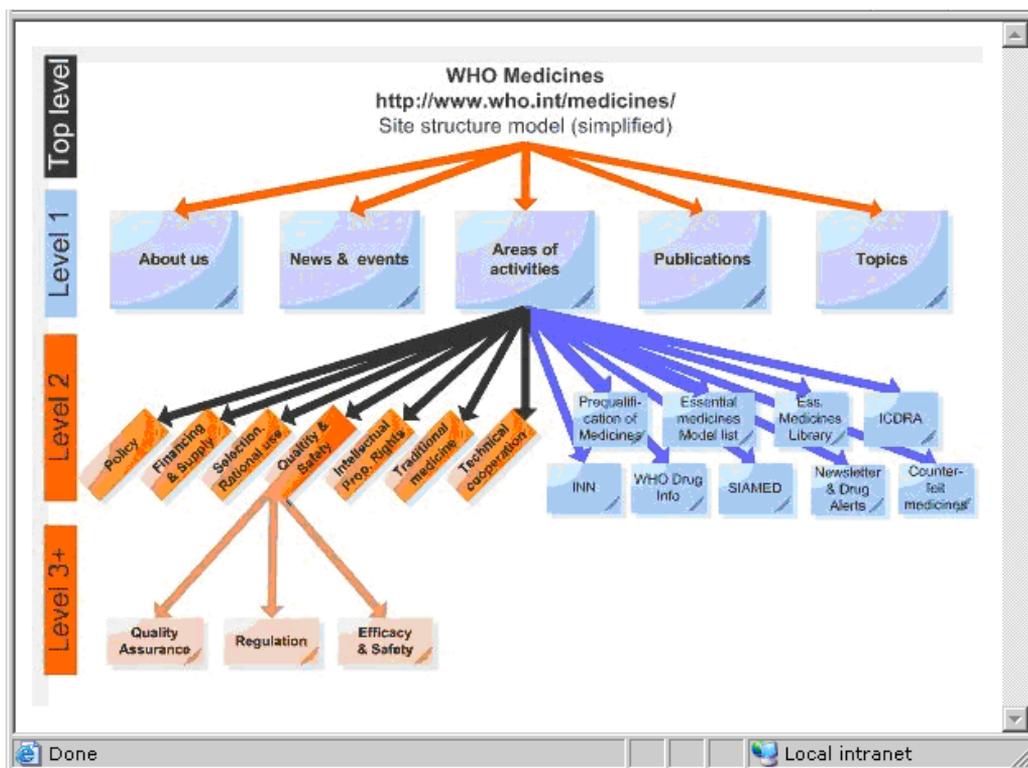
The screenshot shows the WHO Medicines website interface. At the top, there are language options: عربي, 中文, English, Français, Русский, and Español. A search bar is located in the top right corner. The main header features the WHO logo and the text 'World Health Organization'. Below the header, there is a navigation menu on the left with options like Home, About WHO, Countries, Health topics, Publications, Research tools, WHO sites, Medicines home, About us, News and events, Areas of work, Publications, and Topics index. The main content area is titled 'Medicines' and includes a sub-header 'Medicines Policy and Standards, Technical Cooperation for Essential Drugs and Traditional Medicine'. Below this, there is a paragraph describing WHO's goal in medicines. The page also features several featured articles with images and titles: 'Medicines Policy', 'Selection and Rational Use', 'Intellectual Property Rights', 'Technical Cooperation', and 'Traditional Medicine'. A right-hand sidebar contains 'CONTACT US', 'LATEST NEWS', and 'LATEST PUBLICATIONS' sections.

The newly designed website provides direct links to WHO medicines activities, while other sources of disease specific medicines information and treatment guidelines can be accessed through the Medicines Library. Full information is readily obtained through user-friendly tools or specific work areas covering:

Medicines Policy
Quality and Safety
Selection and Rational Use
Technical Cooperation

Financing and Supply Management
Prequalification of medicines
Intellectual Property Rights
Traditional Medicine.

A tiered structure allows access to several related Internet-based information resources. The left-hand menu bar provides the basic site structure and allows the user direct access to information on department structure ("about us"), as well as "news and events", "publications" and, finally, a very useful alphabetical "topics index".



Offering fresh content, the site also includes a number of additional features, including:

Advanced Medicines and WHO site search based on Google™
 An expanded medicines “News and Events” section; and
 Integrated web databases and on-line information retrieval.

The “Publications” section on the site now incorporates a new medicines documentation system containing over 400 documents in English, French and Spanish. The documentation system covers key areas of work and outputs and has the following features:

FULL SEARCHABILITY: With the changeover to HTML, advanced searches across the entire collection will produce not just a ‘hit list’ of document titles to which the search refers, but highlight all occurrences of the term within a text.

MULTILINGUAL: Documents are available in English, French and Spanish. When additional language versions of a document exist, these are indicated by language icons. Clicking on the icon for a language takes the user directly to the same document in the specified language.

DIFFERENT FILE FORMATS: In addition to HTML files, PDF versions of documents have also been included and can be accessed by clicking the icon. Alternatively, the ‘Export to PDF’ feature can be used to create PDF files.

CONTENT FOR COURSES OR REPORTS: The “e-Course builder” feature enables the compilation of an HTML-based document containing a selection of chapters or sections from any number of documents in the system. Once compiled, this document can be further edited or adapted as required.

The English version of the **Essential Medicines Library** is now fully functional. The Medicines Library is designed to link essential medicines included in the WHO Model List to clinical treatment guidelines, the WHO Model Formulary (available in four languages), the International Pharmacopoeia, price information, additional resources and websites accessible throughout WHO and on the Internet.

Other topics of interest accessible through the site are:

Antimicrobial Drug resistance <http://www.who.int/drugresistance/>

WHO Drug Information <http://www.who.int/druginformation>

Prequalification of Medicines <http://mednet3.who.int/prequal/>

MedNet <http://mednet.who.int/> extranet services & International Nonproprietary names (INN)