WHO Drug Information

Contents

Announcement

The 13th International Conference of Drug Regulatory Authorities (ICDRA) will be hosted by the Swiss Agency for Therapeutic Products (Swissmedic) in collaboration with the World Health Organization

The ICDRA will take place in Berne, Switzerland from 16 to 19 September 2008

Updated information will be provided regularly at:
http://www.icdra.ch

or

http://www.who.int/medicines/icdra/en/index/html

Access to Essential Medicines

WHO celebrates thirty years of essential medicines

Essential medicines are those medicines that address the priority health care needs of a given population. Selection is based on health relevance, quality, safety, efficacy and comparative cost-effectiveness. Essential medicines should be available in suitable amounts and dosage forms and provided through a functioning health system. The selection of essential medicines is a cornerstone of national medicine policies.

Essential Medicines List: A primary health care tool

2007 marks the 30th anniversary of the World Health Organization's Model List of Essential Medicines (EML). The EML was created in 1977 with the aim of providing a model for governments to select medicines which address local public health needs and to serve as a powerful tool for the promotion of primary health care by rationalizing the selection and use of medicines as well as their cost.

The EML is revised by a committee of independent experts every two years to reflect developments and new health challenges. The March 2007 version addresses many global priority conditions, such as malaria, HIV/AIDS, tuberculosis, reproductive health and chronic diseases.

Currently, 156 of the 193 WHO Member States have adopted essential medicines lists. Some countries have provincial or state lists as well.

Access to medicines in developing countries is difficult for several reasons. These include poor supply and distribution systems, insufficient health facilities and staff, low investment in health and the high cost of medicines. The EML is a tool that can help manage the purchasing and distribution of medicines and the selection of quality assured and cost-effective products.

- Pharmaceuticals represent 15 to 30% of health spending in transitional economies and 25 to 66% in developing countries.

- In developing countries such medicines are the largest health expense for poor households.

- In 2004, a survey carried out in Uganda showed that among 28 medicines on the country's national essential medicines list only 55% could be found in health facilities where treatment is offered for free. If the inhabitants had to buy the same medicines 'out-of-pocket', prices were found to be 13.6 times higher for branded products and 2.6 times higher for generics than the international pricing reference.

- The Report of the Commission on Macroeconomics and Health (2001) estimates that by 2015 over 10 million deaths per year could be averted by scaling up interventions for communicable and noncommunicable diseases, and maternal and perinatal conditions. The majority of these interventions depend on essential medicines.

Pioneer countries

Mozambique
In 1977, a few months before WHO published the first EML, Mozambique had already created its national pharmacopeia and a list consisting of 430 essential medicines. The country has increased local access to medicines from 10% of the population in 1975 to 80% in 2007.

A WHO survey carried out in 2006, reports that patients interviewed at the dispensing area of public facilities were paying a median of 2 800 Metical for their medicines plus fees — equivalent to a half hour's wage for the lowest paid unskilled government worker.

According to the same survey, among 465 medicine samples tested for regulatory purposes only 34 (7.4%) failed identity or assay.

Peru
In 1960, Peru created a list of basic medicines in an attempt to address at least the most pressing pharmaceutical needs of the population.

In 1971, the country promoted the Basic Medicines Programme, stimulating the creation and use of the first national list of essential medicines.

Sri Lanka
Sri Lanka (formerly Ceylon) created a medicines list for purchase by the state health care system in 1959. In addition, the Ceylon Hospitals Formulary was published providing information for the use of these medicines. They also set up an international procurement system which decreased costs and at the same time increased the availability of these medicines.

In spite of industry opposition, Sri Lanka introduced a state controlled monopoly in 1972, to procure medicines for the entire country through the creation of the State Pharmaceutical Corporation (SPC) thus extending the initiative to the private sector. After 1977, due to pressure from the private sector, the Sri Lankan government granted permission to companies to import multiple brands of medicines.

In 1987, Sri Lanka created the State Pharmaceutical Manufacturing Corporation (SPMC) with the aim of importing raw materials and manufacturing generic essential medicines. Ever since, government resistance to privatization and monopoly on procurement has kept quality as well as prices under control even in the private sector.

A critical factor of Sri Lanka's success is universal education, which has resulted in greater awareness of the importance of health and a strong demand for health services in general. Health professional education and training are tailored to the national medicine supply policy and system, including the essential medicines concept.

Widely recognized and adopted
Many international organizations, including UNICEF and UNHCR, as well as nongovernmental organizations and international non-profit supply agencies, have adopted the essential medicines concept. Essential Medicines Lists guide the international procurement and supply of medicines, schemes that reimburse medicine costs, donations, and local production.

The International Federation of the Red Cross and Red Crescent Societies and Médecins Sans Frontières (MSF) — as well as professional bodies such as the British Medical Association and the International Pharmaceutical Federation (FIP) — have also adopted the essential medicines approach and base their medicine supply system mainly on the EML. The EML has been extensively used to develop international lists for special indications, such as The Interagency New Emergency Health Kit (1998); the UN List of Emergency Relief Items; or Essential Medicines for Reproductive Health (2006).

Source: World Health Organization. http://www.who.int/medicines

Pharmacovigilance Focus

Estrogen therapy and symptoms of parkinsonism: a review using WHO's ADR data base

It has long been known that fewer women are diagnosed with Parkinson disease than men. The seemingly protective effect offered to females against degenerative disease of the central nervous system may relate to estrogen, although the mechanism of action on the dopaminergic system is poorly defined. With an estimated 10–15 million women using oral contraceptives in the United States alone, this review sets out to examine the evidence for a possible relationship between Parkinson disease and estrogens in women.

A review of the current literature available on the topic was performed by consulting Medline and by performing a search of case-reports contained in the World Health Organization's International Drug Monitoring Programme database for possible Parkinson disease-related symptoms that may arise from estrogen therapy. The results, whilst conflicting, seem to establish that estrogen protects women from obtaining the disease, or some features of it. Intensive research is now needed to establish a relationship between estrogen therapy and development of parkinsonism.

Parkinson disease (PD) is a chronic, progressive degenerative disorder that is characterized by the selective degeneration of mesencephalic dopaminergic neurons in the Substantia nigra pars compacta (SNpc) (1). The loss of dopamine afferents results in reduced dopamine being released into the target field of these neurons, the corpus striatum (2) and the manifestation of an extrapyramidal motor dysfunction, characterized by tremor, rigidity, and bradykinesia (3). In recent years, several genes have been linked to autosomally recessive forms of PD. However, the vast majority of PD cases appear to arise sporadically (4) and the exact etiology of the dopaminergic degeneration in these cases remains unknown. A number of mechanisms have been proposed, including the role played by oxidative stress, glutamate-induced excitotoxicity, depleted levels of endogen-ous antioxidants, reduced expression of trophic factors, inflammatory processes and a dysfunctional protein degradation (1, 5). In addition, it has been suggested that exposure to environmental toxins, such as pesticides and herbicides, either alone or in synergy with endotoxic and/or

"Use of WHO's global database to compare hormone replacement therapy and parkinsonian symptoms in women", *a study by Ilse S. Pienaar and William M.U. Daniels, Department of Medical Physiology, University of Stellenbosch, South Africa; I. Ralph Edwards and Kristina Star, Signal Detection and Analysis Department, The Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, Sweden; Karl J. Morten. Nuffield Department of Obstetrics & Gynaecology, University of Oxford, The Womens' Centre, John Radcliffe Hospital, United Kingdom. Reprints of the review can be obtained from: ilse.pienaar@dpag.ox.ac.uk*

genetic predisposing factors, may contribute towards damage sustained by DA neurons (5, 7). This may especially be true when exposure takes place during the developmental period, when neurons are particularly vulnerable.

Several epidemiological studies have reported a 1.5 to 2 times higher incidence and prevalence of PD in men compared to women (7–12) such as US and European studies reporting a male preponderance for PD, (7, 13–15). However, a female preponderance is reported to exist for Parkinson disease in Japan, (16) and discrepancies are regularly reported in terms of incidence, symptoms, medication effects and treatment response (17). Examples of these inconsistencies are a higher prevalence of very late-onset PD found in females (18) and lifetime fluctuations in the progressive course of PD in female patients (19).

The marked sex difference in the rate of the disease suggest that the brain's hormonal environment during adulthood may be an important point of departure in the search for an explanation. It has been suggested that the reproductive female hormones estrogen, progesterone and luteinizing hormone, as is experienced by women during the post-menopausal life-phase, may exert a protective effect within a neuronal environment, with respect to neuronal degeneration, growth, and susceptibility to toxins.

Evidence for this was shown in animal models where an apparent neuroprotective effect was exerted by estrogen when the hormone was administered prior to or coinciding with the toxic insult necessary for simulating symptoms of PD (20–22). Estrogen exerts its effects on the central nervous system (CNS) via both genomic mechanisms (to modulate the synthesis, release and metabolism of neurotransmitters, neuropeptides and neurosteroids), as well as through non-genomic mechanisms, by influencing electrical excitability, synaptic function and morphological features. Such influences may not only exert an influence on the male preponderance observed in a disease associated with the nigrostriatal dopaminergic system, such as PD (23) but may also be pivotal in the pathogenesis of other age-related neurodegenerative diseases, such as Alzheimer disease (24).

Animal studies indicate that estrogen affects the synthesis, release and metabolism of dopamine via its effects on DA uptake (25) sites and may also modulate dopamine receptor expression and function (26), thereby influencing behaviours mediated by the basal ganglia (27). In addition, a neuroprotective effect for estrogen has been demonstrated in animal models of PD that employ neurotoxic insults to selective neuronal populations. For example, this has successfully been demonstrated (28–29) for 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) toxicity in primates, while similar results have been revealed using the 6-hydroxydopamine rat model (20). Furthermore, a loss of dopaminergic neurons in the Substantia nigra of non-human primates exceeding 30% as a result of estrogen deprivation has been reported (30), while chronic estrogen replacement was found to restore dopaminergic function in ovariectomized rats (31).

Although there are a number of reports on the beneficial effects of estrogen on the CNS of animals, human data are scarce and often contradictory (32, 33). Evidence on whether estrogens stimulate or inhibit the human dopaminergic system is inconsistent and ranges from reports that the use of estrogen alone (in the absence of progesterone) may increase the risk of developing PD among women who have undergone a hysterectomy (34), to studies in which no modifying effect had been observed (35).

Such inconsistencies are difficult to explain, especially in light of evidence suggesting that neither dopamine-sensitive cells, located in the originating mesencephalic region nor those in the terminating basal ganglia show the ability to concentrate estrogen (32). Instead, these findings evoke confusion and provide an inadequate foundation for practice guidelines.

Menopause is a normal milestone experienced annually by at least 2 million women in the USA alone (36) and involves the cessation of ovarian secretions, such as estrogen. Due to improvements made in medical care delivery over the past few decades, average life expectancy has increased, accounting for aging of western world populations at a progressive rate (37). However, the average age at which menopause commences and terminates remains constant, so that women can currently expect to live up to one half of their adult lives after the menopausal period (38).

Many women are concerned about the relationship between menopause and health due to reports that post-menopausal estrogen deficiency leaves women more exposed to neurotoxic assault. Furthermore, due to an aging population, an increasing number of people can expect to experience age-related disorders associated with abnormalities of the dopaminergic system, including PD (13). Evidence to encourage such concerns include reports of less severe symptoms during the early phase of PD in women who receive estrogen replacement therapy, a reduced anti-parkinsonian threshold dose for levodopa, (39) and gender differences in terms of symptoms and response to levodopa treatment. One study (40) made use of a 'neuroendocrine challenge', a technique widely used for exploring neurotransmitter tone in humans for detecting the effects of estrogen on the dopaminergic response. The investigators used apomorphine-induced growth hormone (GH) secretion via post-synaptic dopamine (D_2) receptors, located in the median eminence of the hypothalamus (41), to investigate central dopaminergic responsivity in female patients. Their results indicate that post-menopausal women who undergo long-term estrogen therapy, have enhanced GH responses, compared to women who are naive to estrogen therapy, thereby suggesting increased dopaminergic tone. Interestingly, a study has reported a comparatively worse decline in the D_2 dopamine receptor concentration for women over men (42). These receptors generally decline to a significant extent in humans as a result of advancing age, particularly in frontal and basal ganglia brain regions (42).

Realization as to the importance estrogen plays in the development and maintenance of not only the female reproductive system, but its modulatory effect on the CNS as well, has resulted in the pharmaceutical development of a vast range of steroidal and nonsteroidal compounds that interact with the estrogen receptors. Globally, more than 60 million women use oral contraceptive therapy, (43) which entails utilizing either a combination product containing both estrogen and progestin, or single entity products containing progestin only. With circulating estrogen levels diminishing in post-menopausal women, HRT is the standard treatment for restoring decreasing hormone levels as a preventative step against discomfort and possible health problems.

Due to reports emerging during the mid-1970's that postmenopausal women who make use of estrogen alone stand a significantly increased risk of developing endometrial- and breast cancer, (44) progestin, a synthetic version of progesterone, was added to the standard HRT regimen in order to counterbalance the effects of estrogen. In addition, there is evidence linking HRT with a marginally

increased risk of stroke, heart disease and breast cancer (45). An androgen, usually testosterone, may be added to the drug regimen to aid in restoring lowered energy levels, libido and prevent osteoporosis following menopause.

HRT has been applied as a therapeutic tool beyond its original design intention. Attempts are made to include HRT as a therapeutic strategy towards a range of target diseases that primarily affect the reproductive system, including breast cancer and uterine dysfunctions (46), while beneficial effects for the use of HRT have also been reported for treating osteoporosis and coronary artery disease (47). Compounds directed at inducing specific and potent estrogen-receptor activity in non-traditional target tissues, such as the central nervous system (CNS) may also possess therapeutic potential, by either modulating brain neurotransmission or via neuroprotective activity. HRT has been found to protect the CNS against the development of diseases such as Alzheimer disease when administered after menopause (48).

However, a large, randomized, double-blind, placebo-controlled clinical trial of postmenopausal HRT failed to replicate these results (49). Studies performed on human patients suffering from extrapyramidal disorders, such as PD, illustrate estrogen's behaviour-mediating effect on dopamine within the basal ganglia (50), and biochemical evidence suggests that estrogen regulates dopaminergic neurotransmission in the basal ganglia (51, 52). In addition, various gynaecologic benefits are associated with HRT, such as an ability to reduce the incidence of secondary amenorrhoea (53), benign breast neoplasm (54), prevention of iron-deficiency anaemia (55), a reduced risk of endometrial cancer (56–59), prevention of ectopic pregnancy (60–63) the formation of functional ovarian cysts (64), and pelvic inflammatory disease (65).

Valid concerns exist that the substantial hormonal changes associated with natural or surgically-induced menopause may have adverse reactions and contribute towards the initiation and/or development of various diseases. Concern is especially provoked by several studies indicating significantly higher incidence of cardiovascular abnormalities including stroke, due to thrombo-embolism, subarachnoid haemorrhage and cerebral venous thrombosis, in users of oral contraceptives, particularly high estrogen formulations (66).

Similarly, a number of neurological alterations suggesting estrogen involvement have been documented. For instance, it has been postulated that chorea may be due to the direct dopaminergic action of estrogens or due to dopamine accumulating in the brain caused by its competitive binding to the dopamine-degrading enzyme catechol-*o*-methyltransferase (COMT) (66). Further support for estrogen's influence on brain function stems from experiments showing that the expression of COMT is regulated by ovarian steroids (51, 52, 67).

Evidence for a role for estrogen in PD is less clear with some studies suggesting that estrogen replacement therapy may be useful for female patients during the early phases of the disease and before initiating levodopa therapy (68). However, others report only a slight anti-parkinsonian effect to 17ß-estradiol therapy or no beneficial PD effects (70), thereby supporting an anti-dopaminergic effect for estrogens on parkinsonian symptoms (71).

In the absence of investigations to establish insight into the effects that estrogen exerts on the dopaminergic system, especially in terms of long-term therapeutic influences, the beneficial results gained from HRT are seen to significantly outweigh the risks involved, and HRT continues to gain widespread prescriptive

support. The current article outlines the apparent paradox of the effects of estrogens on the CNS with particular reference to whether the provision of hormone replacement therapy will worsen or reduce the chance of PD or PD-like symptoms, or alter specific attributes of the PD syndrome.

Method

The present study is a review of currently available data to assess the relative safety of supplementary hormone therapy to women. The rationale for this is that the number of women reaching their midlife years and beyond who seek professional advice regarding HRT is likely to double. Yet the studies that have investigated the relative safety of estrogen treatment in the context of developing PD-related symptoms are limited. At best the studies are inconclusive with findings suggesting both an associated risk (23, 35) as well as no associated risk for developing the disease (45) being reported. In view of the conflicting evidence, we revisited existing published data, in conjunction with the WHO Programme for International Drug Monitoring, through its Collaborating Centre based in Uppsala, Sweden, to examine the increased risk that HRT may specifically hold for developing PD-related symptoms.

The WHO Programme for International Drug Monitoring database contains approximately 3.7 million case reports of suspected adverse drug reactions that have been filed as reports since 1968, with a total of 81 countries currently participating in the programme (72). Such spontaneous reports provide a first-line surveillance method for the detection of new adverse drug reactions (ADRs). This is extremely useful because of the sizeable population surveyed and the timely reporting of unexpected adverse reactions (73).

A data mining search (74) was performed to extract drug-ADR combinations occurring more frequently than expected. A positive drug-reaction association implies a significant difference from the entire global report (75). The search was done using the anatomical therapeutic chemical (ATC) classification to cover all estrogen-containing compounds. Reports with drugs belonging to any of the following ATC groups were included in the search:

- hormonal contraceptives for systemic use/progestogens and estrogens;
- estrogens/natural and semisynthetic estrogens; synthetic estrogen;
- estrogen combined with other drugs;
- androgens and estrogens;
- androgen alone;
- progestogen and estrogen in combination; and
- progestogens and estrogens in combination.

The following WHO-preferred terms were used during the search for therapy-associated movement disorders: Bradykinesia, Dyskinesia, Hypokinesia, Choreoathetosis, Hypertonia, Tremor, Extrapyramidal disorder and Parkinsonism aggravated. In the WHO adverse reaction terminology, there were 4 terms related to ‘Parkinson disease’. Three subterms were included under the preferred term ‘extrapyramidal disorder’, namely ‘Parkinson syndrome’, ‘Parkinsonism’ and ‘Parkinsonian gait’, while the fourth term was the preferred term ‘Parkinsonism aggravated’, that did not contain additionally included terms.

Results and Discussion

Very few reports of PD per se were revealed during the search, suggesting that PD is either unrecognized as an adverse effect of estrogen-containing compounds or that a weak relationship exists between the two. However, it is acknowledged that under-reporting and

failure to recognize adverse reactions with a long latency are two weaknesses inherent to this particular reporting system.

Reports to the WHO Programme indicate a disproportionately high amount of chorea compared to all other drugs in the database, though this does not reach 95% confidence level significance. Differential diagnosis of chorea, in addition to Sydenham chorea, include Wilson disease; encephalitis; Huntington chorea; drug intoxication; benign familial chorea; pregnancy; systemic lupus erythematosus; Henoch-Schonlein purpura; polycythemia vera; hypocalcaemia; hyperthyroidism; carbon monoxide poisoning; cerebral infarction, and intracranial tumour (76).

Chorea involves rhythmic motor oscillations characterized by brief, irregular muscle contractions that are not repetitive or rhythmic in nature, but rather appear to continually flow from one muscle to the next, often co-presenting with athetosis, adding twisting and writhing movements by the hands, feet, trunk, neck and face, to the already existing disorder. Chorea may be drug-induced and this is the most commonly occurring type of chorea found in practice (78, 79). More than 40% of all PD patients, depending on age and dosage used (80, 81) develop chorea after 5–10 years of continual levodopa use with increasing numbers of patients affected as time elapses (82). It is thought that chorea is due to the drug's ability to stimulate postsynaptic dopamine receptors in a pulsatile fashion, evoking changed responses amongst the neuronal networks that interconnect the basal ganglia with the frontal cortical motor regions (80). Such excessive thalamocortical facilitation thereby overactivates the neurotransmitter dopamine (80).

However, inconsistencies between the proposed model and clinical evidence have been observed, including the absence of increased excitatory thalamocortical drive following pallidotomy, which should effectively worsen chorea (83). Current opinion on what constitutes hyperkinetic movement disorders, such as chorea, maintain that more complex alterations in the temporal and spatial firing pattern of the globus pallidus are responsible for the clinical phenomenon (80, 83, 23, 11, 84). A paradox seems to exist as to the effects of estrogens on the CNS, with particular reference to whether the provision of hormone replacement therapy will worsen or reduce the chance of PD, or alter specific attributes of the PD syndrome.

Following the first report of an association between chorea and oral contraceptives in 1966 (85), various additional case-reports and epidemiology-based studies have revealed chorea to be a rare complication of estrogen-containing oral contraceptive therapy, such as the use of topical vaginal cream containing conjugated estrogen (86). One large-scale study (87) reported that 12% of all patients that participated in the study, developed chorea soon after starting estrogen-containing oral contraceptive treatment, with 6% developing chorea gravidarum and 2% developing the disorder shortly following delivery.

In contrast to certain other drugs found to cause this anomaly and which tend to function at a more universally choreigenic level, OCs prerequisitely require existence of basal ganglia dysfunction in order to induce adverse effects (88). Such adverse drug reactions are only expected to occur as recurring choreic episodes, such as Sydenham chorea, chorea due to systemic lupus erythematosus, chorea gravidarum (89) or when levodopa-induced (80), with the time between initiation of therapy and appearance of choreiform movements varying from 6 days to 9 months (76). This observation supports previous reports that women present more often with tremor than men (77), indicating a mild form of motor deterioration and striatal degeneration.

During future studies it therefore remains essential to consider controlling for such possible variation. The relatively well described incidence of chorea associated with estrogens, is therefore a clear concern to patients using levodopa when chorea is one of the most troublesome adverse effects relating to treatment with that drug. There is a need to know whether there is a potential-stimulating interaction by estrogens.

Summary

There are several ways human studies could be performed with different comparisons made between genders, age groups, with either the use of HRT or not, as well as by carefully differentiating the components of PD. Recent reports of a correlation between estrogen-based therapy and chorea were found to be lacking in recent literature, and large studies on PD with sufficient power to examine the differential effects of estrogen on the PD syndrome have not been conducted.

However, the current review highlights that there is indeed cause for concern in this regard, because of the conflicting results presented, with a definite need for further investigation in order to extrapolate for the relationship between female gonodal hormones and the nigrostriatal dopaminergic system. The absence of evidence for any signal on the adverse effects of estrogen-containing compounds on PD in the WHO database could be interpreted as a failure to recognize a signal of a causative effect or worsened PD, even though the database reflected the known occurrence of chorea as a side-effect to estrogen-based therapy. None the less, the result does not conflict with the possibility that estrogens may protect from all or aspects of the PD syndrome (19).

The regulatory effect of estrogen on the activity of dopamine-containing fibres originating in the midbrain and terminating in the basal ganglia and on dopamine-sensitive cells in the basal ganglia is complex and the mechanism of action is unclear since cells in neither of these regions concentrate estrogen. While estrogen may act indirectly via the catechol-estrogens and prolactin, it has been demonstrated that estrogen can act directly on the striatum also (31). These findings relate to the effects of estrogen on human extrapyramidal disorders. However, estrogen appears to pose only limited efficacy in the treatment of dyskinetic disorders, despite its apparent antidopaminergic effect in humans. Intensified research efforts are called for before agreement can be reached with regards to the locus, direction, or the mechanism of OC and HRT action on basal ganglia function.

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Safety and Efficacy Issues

Perflutren injectable: serious cardiopulmonary reactions

Canada — Perflutren Injectable Suspension (Definity®) is an ultrasound contrast indicated for ultrasound imaging of cardiac structures (ventricular chambers and endocardial borders) and function (regional wall motion) in adult patients with suboptimal echocardiograms. It is also indicated for ultrasound imaging of the liver and kidneys in adult patients. The manufacturer of this product has circulated information pertaining to post marketing reports of serious cardiopulmonary reactions, including fatalities.

As of 30 September 2007, a total of 99 cases of serious cardiopulmonary reactions have been reported to the company, with none reported from Canada. In post-marketing use, four patients experienced fatal cardiac arrests either during or within 30 minutes of administration. Three of the 4 patients had pre-existing conditions, including severe congestive heart failure and one on mechanical ventilation for respiratory failure.

Other uncommon but serious reactions observed during or shortly following administration included cardiac or respiratory arrest, loss of consciousness, convulsions, symptomatic arrhythmias (atrial fibrillation, supraventricular tachycardia, and ventricular tachycardia or fibrillation), hypotension, respiratory distress or cardiac ischemia.

Patients should be assessed for the presence of any condition that precludes Definity® administration and should be monitored during and for 30 minutes following administration, including vital sign measurements and electrocardiography in all patients and cutaneous oxygen saturation in patients at risk of hypoxaemia. Resuscitation equipment and trained personnel should be readily available.

Conditions that preclude administration include:

- Worsening or clinically unstable congestive heart failure
- Acute myocardial infarction or acute coronary syndromes
- Serious ventricular arrhythmias or high risk for arrhythmias
- Respiratory failure
- Severe emphysema, pulmonary emboli or other conditions that cause pulmonary hypertension.

Reference: Health Canada, Medeffect, 18 October 2007 at http://www.hc-sc.gc.ca

Gefitinib: failure of overall survival vs docetaxel

Canada — The manufacturer of gefitinib (Iressa®) 250 mg tablets has informed healthcare professionals taking part in the Iressa® Patient Registry (IPR) of the failure to demonstrate non-inferiority in overall survival versus docetaxel. The results are from a Japanese multicentre, Phase III study in patients with advanced, metastatic, or recurrent non-small cell lung cancer, who failed one or two chemotherapy regimens.

The study failed the primary objective to demonstrate non-inferiority of Iressa® to

docetaxel in overall survival. When compared to docetaxel, some secondary endpoints showed benefit with Iressa® use, but other secondary endpoints did not.

No new safety findings were noted. There were 3 treatment-related deaths due to interstitial lung disease in the Iressa® arm and none in the docetaxel arm. No patients in Canada should receive Iressa® unless they are enrolled in the IPR.

Reference: Communication from Astra Zeneca through Health Canada, Medeffect, at http://www.hc-sc.gc.ca

Rituximab and progressive multifocal leukoencephalopathy

Australia — The Adverse Drug Reactions Advisory Committee (ADRAC) has received a report of the rare neurological disease, progressive multifocal leukoencephalopathy, associated with the use of rituximab (Mabthera®) (1).

Rituximab is an immunosuppressant available in Australia since 1998 for the treatment of certain types of non-Hodgkin lymphoma. Its indications were extended in December 2006 to include use with methotrexate for the treatment of severe active rheumatoid arthritis in patients not responding to, or unable to take, a tumour necrosis factor antagonist.

In December 2006, the US Food and Drug Administration (FDA) noted that two patients had died after treatment with rituximab for systemic lupus erythematosus (2). The cause of death was progressive multifocal leukoencephalopathy (PML), a viral infection of the brain caused by reactivated JC virus. JC virus is a human polyomavirus that causes widespread infection in childhood and is latent in about 80 percent of adults (2).

PML is a rare but devastating disease, occurring in fewer than 1 per 1500 patients with lymphoma treated with rituximab in clinical trials; no cases were reported in approximately 3000 patients with rheumatoid arthritis (3). Symptoms of PML include mental deterioration, confusion, vision loss, difficulty speaking, and loss of balance. PML usually results in death or severe disability. There is no known effective treatment other than to stop medicines that are interfering with the immune system.

In the case reported to ADRAC, a patient with Waldenstrom Macroglobulinaemia presented with altered vision and a new left homonymous hemianopia one month after commencing rituximab. He had a complicated history and had received other immunosuppressive treatment including fludarabine, corticosteroids and irradiation. He died 5 months later, with widespread lesions of PML found at autopsy (1).

Rituximab use is increasing and it is possible that patients will present to GPs when new symptoms develop. Patients treated with rituximab who present with new neurological signs or symptoms should be referred for evaluation. The Precautions/spontaneous reporting sections of the rituximab Product Information have been recently updated to include information relating to PML.

Extract from Australian Adverse Drug Reactions Bulletin Volume 26, Number 4, August 2007.

Reference

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Implanon®: interactions and contraceptive failure

Australia — Hepatic enzyme inducing medicines can reduce the efficacy of contraceptives, including implantable contraceptives, leading to unintended pregnancy.

Medicare Australia data indicate that 370,173 etonogestrel-containing contraceptive implants (Implanon®) have been dispensed since 2001. The Adverse Drug Reactions Advisory Committee (ADRAC) database contains 594 reports concerning Implanon®, 32 of which describe a suspected interaction between Implanon® and another medicine, resulting in unintended pregnancy.

Medicines implicated in a possible interaction with Implanon® leading to contraceptive failure include carbamazepine (26), phenytoin (4), methylphenobarbital (1) and rifampicin (1). All but 1 of these interactions involved medicines used to treat epilepsy. The 4 interacting medicines are potent inducers of CYP3A4 and other phase I and phase II enzyme systems in the liver. This enzyme induction is likely to reduce plasma concentrations of etonogestrel which, similar to other contraceptive steroids, is catalysed by CYP3A4.

Other medicines likely to interact with etonogestrel and thus possibly reduce its contraceptive effect or lead to breakthrough bleeding include primidone, oxcarbazepine, rifabutin, griseofulvin and products containing St John's wort. Maximal enzyme induction is generally not seen before two to three weeks but may then be sustained for at least four weeks after cessation of therapy with these medicines.

The Product Information advises that women receiving short-term treatment with any of the above medicines or other hepatic enzyme inducing medicines should temporarily use a barrier method in addition to Implanon®, i.e. during the time of concomitant medicine administration and for at least seven days after discontinuation. For women taking rifampicin, an additional barrier method should be used during the time of rifampicin administration and for 28 days after its discontinuation.

Prescribers are reminded that in women receiving long-term treatment with hepatic enzyme inducing medicines, the approved prescribing information recommends Implanon® should be removed and another, nonhormonal, contraceptive method should be used.

Extract from Australian Adverse Drug Reactions Bulletin Volume 26, Number 4, August 2007.

Atypical antipsychotic agents and extrapyramidal effects

Australia — It has been suggested that the atypical antipsychotic agents clozapine, risperidone, olanzapine, aripipazole and quetiapine may have lower propensity for causing extrapyramidal side effects (EPS) when compared with older antipsychotic agents such as haloperidol, chlorpromazine and thioridazine (1,2) However, studies comparing the incidence of EPS between the older and newer agents are often confounded, especially by previous exposure to older agents (2).

Adverse Drug Reactions Advisory Committee (ADRAC) data were searched for reports of EPS in association with the newer antipsychotic agents, using terms relating to nervous system disorders and movement disorders. The number of these reports, as well as total number of reports involving the medicine, is shown in the Table overleaf. Reports for haloperidol are included for comparison.

Medicine	Total reports	EPS reports	(% of total)
Aripiprazole	147	33	(22.4)
Risperidone	812	159	(19.6)
Quetiapine	315	42	(13.3)
Olanzapine	1203	126	(10.5)
Clozapine	3775	70	(1.9)
Haloperidol	753	321	(42.6)

These data should be interpreted with caution. As with most data from spontaneous reporting, the data do not take into account factors influencing reporting rates, such as level of usage and intensive post-market safety monitoring programs. Reports with the newer agents are also likely to be confounded as described above, and ADRAC data for haloperidol are likely to be substantially more incomplete and limited than data for the newer agents. Therefore, the relative numbers of EPS reports shown in the Table do not necessarily reflect relative risk between these agents.

The most common reactions described in reports with the newer antipsychotic agents include dystonias, dyskinesias, akathisia and other non-specified EP disorder. At the time of reporting, about one third of patients experiencing EPS had not recovered, with no distinction between medicines in this regard.

Extract from Australian Adverse Drug Reactions Bulletin Volume 26, Number 4, August 2007.

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Thiazolidinediones and reduced bone density

Australia — Thiazolidinediones include rosiglitazone (Avandia® and Avandamet®) and pioglitazone (Actos®). These medicines act to increase insulin sensitivity and are widely prescribed to treat type II diabetes mellitus. Recent evidence suggests thiazolidinediones are associated with an increased risk of peripheral fractures in post-menopausal women.

The ADOPT study (1) was a randomized, double-blind, parallel group study that followed the progression of 4360 recently diagnosed patients with diabetes mellitus for a median of 4.0 years. The incidence of fractures in women taking rosiglitazone was 9.3%, compared with 5.1% in those taking metformin and 3.5% in those taking glibenclamide. The majority of fractures in these patients were in the humerus, hand, or foot. The incidence of fractures of the hip or spine in women and the incidence of fractures in males were similar among the 3 treatment groups.

A sponsor-initiated review of fracture risk in patients treated with pioglitazone for up to 3.5 years also found more fractures in female patients taking pioglitazone than those taking a comparator. There was no increased risk of fracture identified in men.

The sponsors of rosiglitazone and pioglitazone have updated the product infor-

mation documents for these medicines and issued letters to healthcare professionals describing the above findings.

The mechanism for increased fracture risk was examined in a 14 week study in 50 healthy postmenopausal women in New Zealand (2). This study showed reductions in markers of bone formation in women taking rosiglitazone 8 mg/day compared with placebo. These changes were evident after 4 weeks and persisted for the duration of the study. There were also small reductions in hip and lumbar spine bone density in women taking rosiglitazone.

The full clinical significance of these recent findings is yet to be determined. However, the risk of fracture should be considered for all patients, especially women, taking or being considered for treatment with thiazolidinediones. For these patients, as for all others with type II diabetes mellitus, attention should be given to assessing and maintaining bone health according to current standards of care.

Extract from Australian Adverse Drug Reactions Bulletin, Volume 26, Number 5, October 2007.

Reference

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Renal impairment with zoledronic acid

Australia — There is a well-known risk of deterioration in renal function with intravenous bi-sphosphonates administered at a rapid infusion rate. The Adverse Drug Reactions Advisory Committee (ADRAC) has received few reports of renal impairment or failure with pamidronate and the oral bisphosphonates risedronate and alendronate, but there is a significant number with zoledronic acid (31 from a total of 268 reports for this drug). While the deterioration in renal function with zoledronic acid (Zometa®) was usually acute, in many cases it did not appear to be related to a rapid infusion rate.

The 31 reports in association with zoledronic acid describe either renal failure (16) or renal impairment (15). It was the only suspected drug in 20 of the 31 reports. Interstitial nephritis was described in 3 of the reports. Zoledronic acid was being used for a variety of indications with multiple myeloma (13 cases) the most common but also breast cancer (5), prostate cancer (4), plasmacytoma, malignant melanoma, osteoporosis, bone metastases and osteomyelitis (1 case each). Only 4 reports did not specify the reason for use.

ADRAC reminds prescribers of bisphosphonates to pay close attention to risk factors for renal impairment and to adhere strictly to the instructions for use.

Extract from Australian Adverse Drug Reactions Bulletin, Volume 26, Number 5, October 2007.

Epoetins: unexplained excess mortality

European Union — The European Medicines Agency (EMEA) has recently reviewed the safety of epoetins. These medicines are used for the treatment of anaemia in patients with chronic renal failure and for the treatment of patients with non-myeloid malignancies receiving chemotherapy (1).

The safety review was initiated because data from recent clinical trials show a

consistent unexplained excess mortality in patients with anaemia associated with cancer who have been treated with epoetins.

In addition, the results of two studies and a meta-analysis have recently been published suggest that treatment of anaemia with epoetins in patients with chronic kidney disease to achieve relatively high target haemoglobin concentrations may be associated with an increase in the risk of mortality and cardiovascular morbidity.

EMEA's Committee for Medicinal Products for Human Use (CHMP) and its Pharmacovigilance Working Party (PhVWP) concluded that the benefits of these products continue to outweigh their risks in the approved indications, but recommended changes to the product information:

- Changes to the 'Indication' section (section 4.1), saying that epoetins should be used in the treatment of anaemia only if associated with symptoms.

- Changes to the 'Posology' section (Section 4.2), stipulating a uniform target haemoglobin range for all epoetins of 10 g/dL to 12 g/dL with a warning not to exceed a concentration of 12 g/dL.

- Changes to the 'Special Warnings and Precautions for Use' section (Section 4.4), adding an explanation that trials have shown a small unexplained excess mortality in association with high target haemoglobin concentrations and they have not shown significant benefits attributable to the administration of epoetins to increase haemoglobin concentration beyond the level necessary to control symptoms of anaemia and to avoid blood transfusion.

- Changes to the 'Pharmacodynamic properties' section (section 5.1) to include new information on results of clinical trials which have shown significant excess mortality in patients who have anaemia associated with various common cancers who received epoetins compared with those who did not receive epoetins.

The changes will now be implemented throughout the European Union. The EMEA has requested all Marketing Authorization Holders for centrally authorised epoetins to submit an application for a type II variation to the marketing authorization. For medicinal products that are authorized at the level of the Member States, the national competent authorities will take further action as appropriate.

The CHMP also identified a need to increase scientific knowledge on the effect of epoetins. Marketing Authorization Holders have been asked to combine all available patient-level data jointly and to assess the functional activity of epoetin receptors in different tumour types, and at different stages in the life-cycle of tumour evolution.

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Contraindicated use of sibutramine and cardiovascular reactions

Canada — Sibutramine (Meridia®), a serotonin and norepinephrine reuptake inhibitor, is an antiobesity agent marketed in Canada since February 2001.

Sibutramine is indicated as adjunctive therapy within a weight management programme for obese patients (1). The Canadian product monograph of sibutramine includes several contraindications. Noncompliance with contraindications could result in serious adverse reactions (ARs).

Health Canada continues to receive reports of ARs in patients using sibutramine who have contraindications. Between 2001 and 2007, 65 reports of cardiovascular ARs suspected of being associated with sibutramine were received. Thirteen of these reports involved patients with at least 1 contraindicated condition.

In 2002 and 2003, international regulatory actions were taken, including safety notices, concerning cardiovascular ARs associated with sibutramine (2, 3, 4). Health Canada and other foreign regulatory agencies reviewed the safety of sibutramine and concluded that the benefit-risk profile of sibutramine remained favourable (4).

Extract from Canadian Adverse Reaction Newsletter, Volume 17(4), 2007.

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Gadolinium–containing contrast agents: nephrogenic systemic fibrosis

Canada — Gadolinium (Gd)-containing media are used to enhance the contrast of magnetic resonance images. Those authorized for sale in Canada include Magnevist®, Omniscan®, OptiMARK®, Gadovist®, ProHance®, MultiHance® and Vasovist.

Nephrogenic systemic fibrosis (NSF), also known as nephrogenic fibrosing dermopathy (NFD), is a systemic disorder whose most prominent and visible effects are on the skin (1). It is associated with significant morbidity (2 3). The fibrosis can extend beyond the dermis and involve subcutaneous tissues, muscles and internal organs (2 ,3). The disease was first described in the medical literature in 2000,(4) but the first case was reported in 1997 (2, 4). To date, NSF has been observed only in patients with kidney disease (1).

Internationally, cases of NSF have been observed with 5 different Gd-containing contrast agents (5), and a causal association has recently been suggested (6). In March 2007, Health Canada communicated this safety concern to the public and health professionals (2, 3). As of June 27, 2007 (see *WHO Drug Information*, **21**(1) 15, 2007), 5 cases of NSF suspected of being associated with Gd-containing contrast agents have been

reported in Canada. This recently discovered disease is currently not described in the Canadian product monographs for these agents.

The association between NSF and the use of Gd-containing contrast media needs to be characterized further. In particular, are other patient populations at risk for NSF (e.g., neonates)? Does the risk vary according to the nature of underlying renal disorder? What is the role of dialysis in the prevention and treatment of NSF?

Valuable information could be obtained from adverse reaction (AR) reports. Spontaneous reporting can be useful to identify the clinical spectrum of the drug-AR pair, the patient subtypes and medical circumstances associated with a suspected AR (7). It can also provide clues to the mechanism of action whereby a product can lead to an AR (7). The addition of clinical information in reports, such as the duration of kidney disease and its underlying cause, laboratory values (e.g. glomerular filtration rate), the type and dose of the contrast agents, and concomitant conditions and medications, is important to help characterize the risk factors of NSF.

Extract from Canadian Adverse Reaction Newsletter, Volume 17(4), 2007.

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Swedish Adjustable Gastric Band: incidents leading to explantation

Canada — The Swedish Adjustable Gastric Band (SAGB) is an implantable, adjustable gastric band indicated for use in the treatment of morbid obesity in adults (1). It consists of a reinforced silicone gastric band fitted around the stomach and an injection port placed under the skin and connected to the band by tubing. The SAGB is designed to reduce food intake and can be inflated or deflated as needed after implantation to meet weight-loss requirements without the need for further surgery. The SAGB was originally licensed for sale in Canada in November 2002. A modified version of

the device, the SAGB Quick Close (SAGB-QC), was added to the licence as part of a device licence amendment in August 2004 (2).

Although band erosion is listed among the possible adverse events (2), the device labelling for patients states that the overall rate of re-operation is low and that extensive use of the SAGB has led to a method where failure is uncommon (3). By definition, band erosion is "a situation where a part of the band has eroded through the full-thickness gastric wall and migrated into the lumen (4). This represents a total failure of the gastric banding procedure (5).

Health Canada has received 19 reports of incidents suspected of being associated with the SAGB and 17 with the SAGB-QC. Thirteen of the 36 reports necessitated removal of the band. Other reports described incidents such as band slippage, band leakage, abscess, dysphagia and regurgitation. In 35 of the 36 reports, band explantation was reported as an outcome.

Since band erosion is often asymptomatic or only mildly symptomatic initially and since the condition is best diagnosed by gastroscopy, which may not be included in the follow-up of asymptomatic patients, the true incidence of band erosion is underestimated in the literature and its diagnosis can be markedly delayed (4, 5). Moreover, band erosion is associated with dense scarring and distortion of tissues, which can complicate revision procedures (5).

The complication rates and outcomes associated with SAGB and reported in the literature are variable. Although the authors of some studies have concluded that use of the SAGB demonstrates acceptable levels of safety and effectiveness (6, 7), others have reported high long-term complication and failure rates and poor long-term outcomes (4, 5). The medical literature suggests that alternative treatment options should be considered and gastric banding should be performed only in carefully selected and fully informed patients (5).

Extract from Canadian Adverse Reaction Newsletter, Volume 17(4), 2007.

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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.

Regulatory Action and News

Influenza virus vaccines: Southern hemisphere 2008

World Health Organization — It is recommended that vaccines for use in the 2008 influenza season (Southern hemisphere winter) contain the following:

- an A/Solomon Islands/3/2006 (H1N1)-like virus (A/Solomon Islands/3/2006 is a current vaccine virus):
- an A/Brisbane/10/2007 (H3N2)-like virus;
- a B/Florida/4/2006-like virus.

As in previous years, 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.

Reference: World Health Organization. *Weekly Epidemiological Record*, 2007;**82**: 351

Withdrawal of cough medicines containing clobutinol?

European Union — Following a review of the safety of clobutinol-containing cough medicines (Silomat®), the European Medicines Agency (EMEA) has concluded that the risks of these medicines outweigh the benefits and has recommended that marketing authorizations be withdrawn.

Silomat® is available without a prescription in a number of EU Member States for the short-term treatment of irritable, non-productive cough..

Having considered all available evidence, it was concluded that the use of clobutinol is associated with a risk of prolongation of the QT interval which is known to be linked to fainting and disruption of the heart rhythm, especially when taken in higher doses. The opinion will now be sent to the European Commission for the adoption of a decision applicable in all EU Member States.

Reference: Press release, Ref. EMEA/480863/2007. London, 18 October 2007. http://www.emea.europa.eu

Rimonabant warning: psychiatric conditions

European Union — The European Medicines Agency (EMEA) has recommended contraindicating rimonabant (Acomplia®) in patients with ongoing major depression or who are being treated with antidepressants, because of the risk of psychiatric side effects.

Doctors in the EU have already been warned about this since June 2006 but the Agency's Committee for Medicinal Products for Human Use (CHMP) has now recommended upgrading this warning. Acomplia® has been authorized in the EU since June 2006 as an adjunct to diet and exercise for the treatment of obese or overweight adult patients. Psychiatric side effects, in particular depression, were identified as the main safety issue at the time of approval. They were reflected in the medicine's product information as a warning that doctors should not prescribe Acomplia® in patients with uncontrolled serious psychiatric conditions such as major depression.

At the 16-19 July 2007 meeting, the CHMP concluded that the benefits of Acomplia® continue to outweigh its risks, except in patients with ongoing major depression or those taking antidepressants.

Reference: Press Release, Doc. Ref. EMEA/329826/2007, London, 19 July 2007 available at www.emea.europa.eu

United States of America —Rimonabant is a first in class cannabinoid receptor 1 (CB1) antagonist/inverse agonist for weight management. The Food and Drug Administration's Endocrinologic and Metabolic Drugs Advisory Committee met on 13 June 2007 to discuss an ongoing data review. The Committee decided that more detailed long-term safety information with larger patient groups was needed with regard to neurological and psychiatric side effects associated with the drug including seizure, depression, anxiety, insomnia, aggressiveness and suicidal thoughts.

Reference: http://www.fda.gov

Lumiracoxib registration cancelled

Australia — The Therapeutic Goods Administration (TGA) has cancelled the registration of the osteoarthritis drug, lumiracoxib (Prexige®) because of serious liver side effects associated with the use of the drug.

Lumiracoxib is a cox-2 inhibitor indicated for symptomatic relief in the treatment of osteoarthritis, relief of acute pain, including post-operative pain and pain related to dental procedures and relief of pain due to primary dysmenorrhoea. It was first approved in Australia in July 2004 and listed on the Pharmaceutical Benefits Scheme (PBS) in 2006. As of 10th August 2007, the TGA has received 8 reports of serious liver adverse reactions to the drug, including two deaths and two liver transplants.

The Adverse Drug Reactions Advisory Committee (ADRAC) has recommended the cancellation of registration due to the severity of the reported side effects.

Reference: Media statement, 11 August 2007 at http://www.tga.gov.au

Lumiracoxib: withdrawal of higher doses

New Zealand — The Medicines and Medical Devices Safety Authority, Medsafe, has withdrawn supply of 200 mg and 400 mg tablets of the cox-2 anti-inflammatory medicine lumiracoxib (Prexige®).

The decision has been reached after Medsafe reviewed local and international safety data relating to reports of severe liver damage in patients using this medication at doses of 200 mg and above. In making the decision, Medsafe discussed the overall risks and benefits of the use of Prexige® with medicines regulators in Australia, Singapore and the United Kingdom.

Medsafe also reviewed the safety of Prexige® 100 mg indicated for use in osteoarthritis. The data available from clinical trials and reported side effects in the United Kingdom, Europe, Canada or South America indicate that severe liver damage with Prexige® 100 mg/day is rare. The frequency with which liver damage is reported for Prexige® 100 mg does not appear to be significantly different from that seen for other anti-inflammatory medicines.

Medsafe has accepted the interim advice of the Medicines Adverse Reactions Committee (MARC) that Prexige® 100 mg should remain on the market and its safety be closely monitored.

Reference: Communication from Medsafe, 21 August 2007, at http://www.medsafe.govt.nz/hot/alerts.asp

Ixabepilone approved for advanced breast cancer

Unites States of America — The Food and Drug Administration (FDA) has approved ixabepilone (Ixempra®), a new anti-cancer treatment, for use in patients with metastatic or locally advanced breast cancer who have not responded to certain other cancer drugs. Ixabepilone is administered by intravenous infusion.

Ixabepilone was approved for use in combination with another cancer drug, capecitabine, in patients who no longer benefit from two other chemotherapy treatments. These prior treatments included an anthracycline (such as doxorubicin or epirubicin) and a taxane (such as paclitaxel or docetaxel). Ixabepilone was also approved for use alone in patients who no longer benefit from an anthracycline, a taxane and capecitabine.

Ixempra has been shown to bind to cancer cell microtubules, which are structures within cells that help to support and shape them. Microtubules also play a role in cell division. The safety and efficacy of ixabepilone in combination with capecitabine were evaluated in 752 patients in a randomized clinical trial comparing the combination to capecitabine alone. This combination therapy demonstrated improvements in delaying cancer progression or death compared to capecitabine alone.

Ixabepilone's significant side effects included peripheral neuropathy (numbness, tingling or burning in the hands or feet) and bone marrow suppression. Other commonly observed toxicities included constipation, nausea, vomiting, muscle paint, joint pain, fatigue and general weakness.

Women taking ixabepilone should avoid taking drugs that are strong inhibitors of CYP3A4.

Ixabepilone should not be taken by women who have had severe allergic reactions to drugs that contain Cremophor or its derivatives, or by women who have baseline bone marrow suppression determined by low white blood cell or platelet count.

The combination of Ixempra® and capecitabine should not be given to patients with moderate or severe liver impairment due to the increased risk of toxicity and death.

Reference: *FDA News*, 22 October 2007 at http://www.fda.gov

Second-generation smallpox vaccine approved

United States of America — The Food and Drug Administration (FDA) has licensed a new vaccine to protect against smallpox, a highly contagious disease with the potential to be used as a deadly bioterror weapon.

A worldwide vaccination programme eradicated smallpox in the population. The last case of naturally occurring smallpox in the USA was in 1949 and the last case in the world was reported in Somalia in 1977. Known stockpiles of the virus are kept only in two approved labs in the United States and Russia.

Smallpox is caused by the variola virus, a virus that emerged in human populations thousands of years ago. It spreads through close contact with infected individuals or contaminated objects, such as bedding or clothing. There is no FDA-approved treatment for smallpox and the only prevention is vaccination.

Because ACAM2000 contains live vaccinia virus, care must be taken to prevent the virus from spreading from the inoculation site to other parts of the body, and to other individuals.

Reference: *FDA News*, 1 September 2007 at http://www.fda.gov

Regulatory updates

European Union — A summary of recent regulatory developments is available from the European Commission.

B.1.1.2 Notice to applicants for medicinal products for human use
EudraLex Vol 2A, Chapter 3 - Community Referral (for human medicinal products) (revised version reflects the current legal framework for referral procedures)

EudraLex Vol 2A, Chapter 7 - General Information (Revision from July 2007) (revised verions includes updated information from different EU Member States and contains a major update of section 3.2 "National, Mutual Recognition and Decentralised Procedures: "additional data" requested)

EudraLex Vol 2C - Guideline on the packaging information of medicinal products for human use authorized by the Community (Revision 12, August 2007) (Remark: Revision 12 was published shortly after Revision 11 in order to include corrections related to the requirements by Italy; revision 11 has been amended to include updates requested by Italy and Sweden)

EudraLex Vol 6A, Chapter 3 - Community Referral (for veterinary medicinal products). (revised version reflects current legal framework for referral procedures)

A.4.6.1 Compassionate Use
According to Art. 83 of Reg. 726/2004 – Definition, Requirements and Procedure.

A.4.6.1.1 Principles of Application of the Compassionate Use Provision.

A.4.6.1.2 Compassionate Use Procedure

CHMP Guideline on Compassionate Use.

In July 2007 the "Guideline on Compassionate Use of Medicinal Products, Pursuant to Article 83 of Regulation (EC) No. 726/2004" was finally adopted by CHMP and implemented on July 19, 2007. It aims at providing guidance and explanations as well as definitions in relation to the criteria and the procedure foreseen in Art. 83 of Regulation (EC) No. 726/2004 and to give information regarding the documentation which has to be submitted. Chapter 4.6.1 has accordingly been supplemented and the presentation of the principle of compassionate use has been extended by Chapters 4.6.1.1 and 4.6.1.2.

A.2.4.3 Inspections Unit of the EMEA
A.2.4.3.1 Responsibilities of the Inspection Unit
A.2.4.3.2 Inspectors Working Groups

EMEA Inspections Unit - GMPD and GCP Inspectors Working Groups - Mandate and Objectives. Shortly after the entering into force of the new European Marketing Authorization System Ad hoc Inspection Services Groups were set up for the sectors of GMP and GCP. At the end of 2006, the Ad Hoc Inspection Services Groups changed names and became "Inspectors Working Groups". Mid 2007, the two Inspector Working Groups published documents on their mandate and objectives. These documents give reason to extend the description of the EMEA Inspections Unit, updating Chapter A 2.4.3 and extending it by Chapters A 2.4.3.1 and 2.4.3.2.

Reference: Informatio available at http://www.drugregulatoryaffairs.eu

Generic Medicines

Generic substitution in Jamaica: challenges to improving effectiveness

In 1993, an Amendment to the Pharmacy Act introduced generic substitution of innovator brands to Jamaica. Although the Amendment gives prescribers the opportunity to indicate "no substitution" on prescriptions, implementation of the generic medicines policy has been largely hindered by doubts concerning therapeutic equivalence. In addition, reservations among many physicians and pharmacists have been observed concerning implementation of the policy.

This review summarizes information collected among health professionals and patients in Jamaica on the knowledge and perceptions surrounding generic substitution of medicines. It concludes that only through evidence-based awareness programmes and responsive pharmacovigilance systems will physicians, pharmacists and the public gain confidence in the concept of generic substitution.

Offering patients generic substitutes to innovator brands of drugs is an encouraged practice of many countries because of the cost saving benefits that can be gained to patient management [1–5]. In 1993, out of a need to reduce the cost of drugs to patients, the Ministry of Health in Jamaica amended the Pharmacy Act, to mandate pharmacists to offer all patients substitution of innovator brands of prescription drugs with less expensive generic brands, thus allowing the patient to choose [6]. Along with the authority given to pharmacists, the amendment additionally allowed physicians to request "no substitution" of innovator brand by generic, or a generic brand by another brand.

In Jamaica, the pharmaceutical market can be quite complex to assess, as many groups are involved and the success of mandates to encourage generics involves much more than a reliance on cost benefit. In a number of cases, generics have been assessed as therapeutically inequivalent [7] and this has had a negative influence on perceptions among health professionals. In 2003, a newspaper article in the *Jamaica Gleaner* reported that both physicians and pharmacists expressed dissatisfaction with generic substitution as mandated by the Pharmacy Act because generics were plagued with incidents of therapeutic inequivalence [8].

In 2006, The Fair Trading Commission, in collaboration with The Consumer Affairs Commission and The University of Technology, examined some of the issues that influenced the sale of innovator and generic products by conducting surveys among patients, physicians and pharmacists. These surveys involved the use of validated questionnaires, comprising

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adequately represented sample sizes and proportionately stratified island-wide groups (i.e. Kingston Metropolitan area, other towns and rural areas) [9]. The results suggest that, in 2006, the perception that generics are therapeutically inequivalent is still of concern among physicians and pharmacists. This will presumably affect acceptance of substitutability and success of the Amendment. This review discusses some of the findings related to knowledge of generic drugs by patients and the prevailing lack of confidence that physicians and pharmacists have in substitutability and proposes some action points.

Patient understanding of the generic concept

This component of the survey was conducted among patients, eighteen years and older (N=1030). The majority did not fully appreciate the term "generic medicine", as 63.6% (N=1,020; non-responsive=10) had either never heard the term or were familiar with it, but not sure what it meant. Therefore, most patients were not adequately informed about the difference or similarities between innovator and generic medicines. Interestingly, of those who were familiar with and understood the term (N=371), a little less than half stated only that gener-

Figure 1. Defining generic medicines

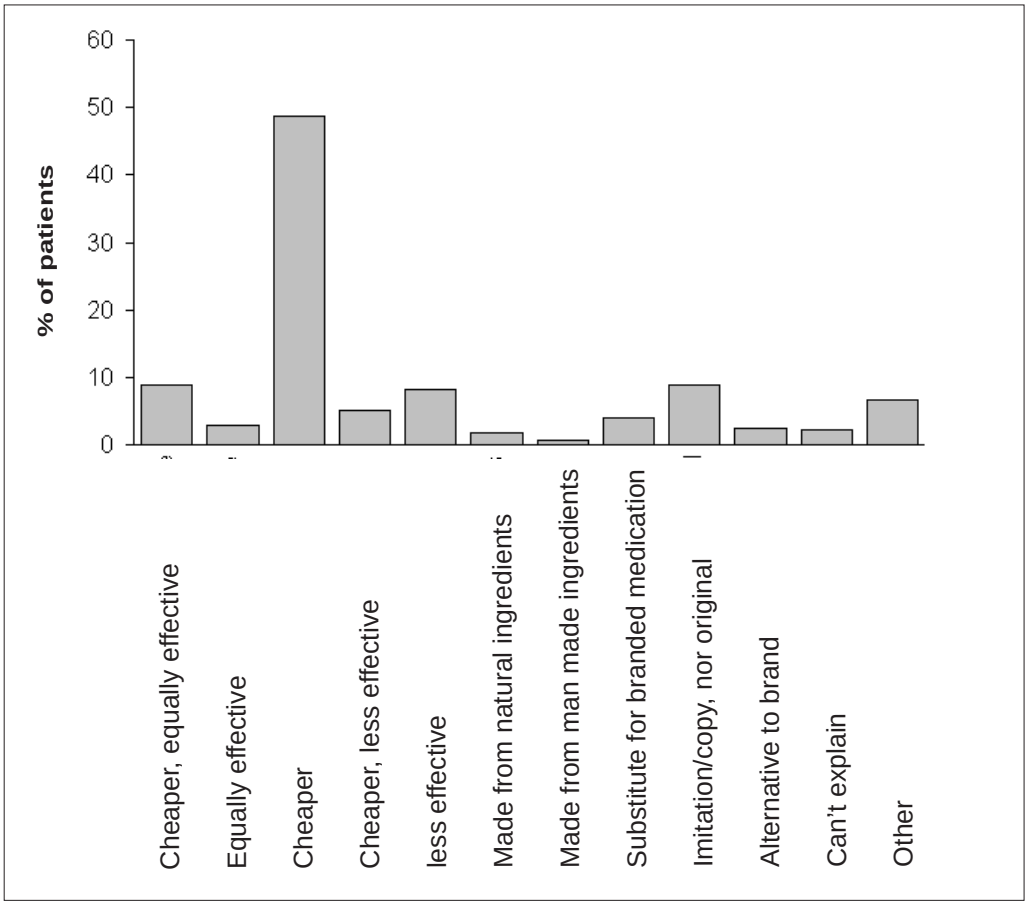


Table 1. Patients: credibility of information sources

Information source	Number of patients (Total = 371)*
Physician	288
Pharmacist	35
Family/Friend	16
Drug manufacturer/importer	12
Ministry of Health	13
Internet	5
Testimonials (word of mouth by other users of medication)	3

** Values in columns do not balance because of non-responders*

ics were cheaper, suggesting that there was a lack of appreciation that generics are expected to provide similar efficacy to that of the innovator (See figure 1).

Patient acceptance of substitution was not significantly influenced by income, health insurance coverage or whether they were compliant to drug therapy. Most of the patients who understood the term generic indicated that physicians and pharmacists were their most credible source of information (Table 1). Additionally, the majority indicated that they would not request substitution of prescribed medicines, whether it be innovator or generic (Figure 2). Therefore a patient's choice to accept substitution with generic medicines will depend on the confidence their physician has in generic products and particularly of therapeutic equivalence. This is supported by pharmacists.

Physician views on therapeutic equivalence

Surveyed physicians (N=242) represented 10% of registered physicians as at 2005. The majority were males (66.8%), practising for over ten years (52.8%) and writing between 10 to 20 prescriptions per weekday (33.1%) of which 50% would be written for generic medicines. When physicians were asked about their perception of therapeutic equivalence

Figure 2. "My doctor knows best"

Patients who understood the term "generic medicine" were asked if they would request substitution of a medicine prescribed by their physician.

A. Patients who would request generic medicine at the pharmacy although physician prescribed innovator (N=355; total non-respondents=16)

Yes = 19.7%
No = 65.4%
Why no:

Reason	No. patients
My doctor knows best	181
It would not be safe to do so	18
Other reasons	32
Non-respondents	4

B. Patients who would request innovator medicine at the pharmacy although physician prescribed generic (N=361; total non-respondents=10)

Yes = 14.4 %
No = 73.4%
Why no:

Reason	No. patients
My doctor knows best	215
It would not be safe to do so	11
Other reasons	34
Non-respondents	2

(N=238; non-respondents=4), 45% indicated that they believed generics were therapeutically equivalent (Figure 3). However, more than 25% indicated doubt, based mainly on the reputation of the manufacturer or quality of the generic drug. This demonstrates an uncertainty regarding the ability of generics to substitute for innovators.

Pharmacist views on efficacy

Pharmacists located in thirty-six pharmacies, representing 10% of pharmacies registered as at 2005, were surveyed. The majority of respondents were females (75%), practising for more than 10 years (47.25%) and filling 30–40 prescriptions on a weekday (22.2%). Pharmacists were specifically asked to give views on the efficacy of generics when compared with innovators. The majority indicated a lack of confidence in generics, as only 44.4% thought they were of the same efficacy as innovators, and this perception was based mainly on feedback from patients (Figure 4). Fourteen of the 36 pharmacists indicated doubt in efficacy due to factors such as the individual situation of a patient, type of illness, manufacturer's reputation and quality of the generic product/excipient.

Challenging awareness

Most physicians indicated a need to increase awareness of the advantages of generic medicines in Jamaica (61.6%, N=242). Pharmacists expressed similar sentiments and indicated that the greatest need was among patients. They suggested that strategies to increase awareness should involve better provision of information to patients by physicians and pharmacists. Because of the trust patients place in health professional advice, any doubt in the value of generics among physicians and pharmacists should be addressed, while there is an urgent need for increased confidence in the therapeutic equivalence of generics.

For such an effort to succeed, knowledge of where these groups obtain credible information is a key. Both pharmacists and physicians were asked to list their top source of credible information. Pharmacists indicated that they relied mainly on medical journals, as well as drug manufacturers, through seminars and their

Figure 3. Physician perceptions and therapeutic equivalence:

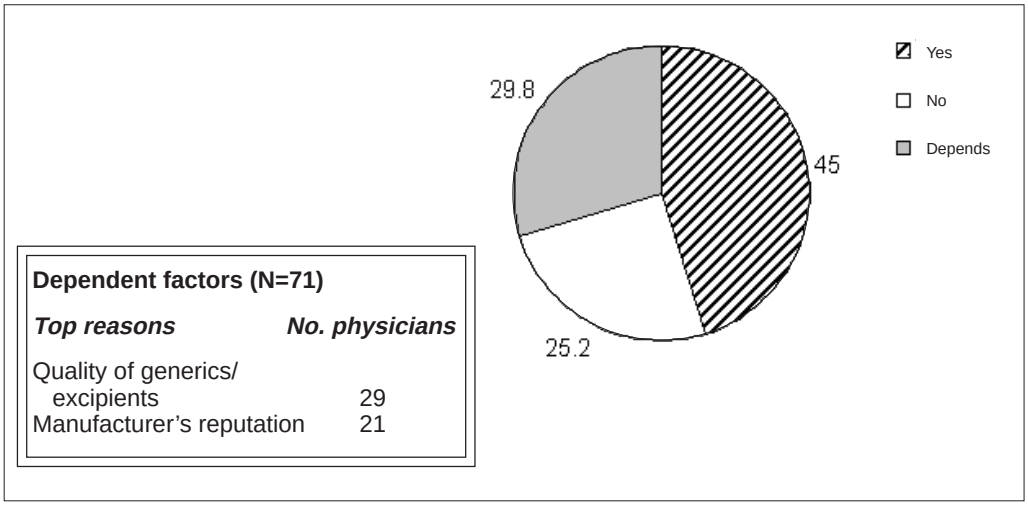
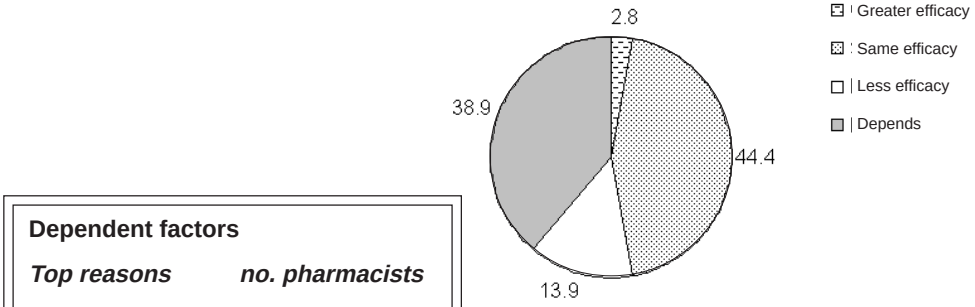


Figure 4. Pharmacist perceptions of generic efficacy



Dependent factors

Top reasons	*no. pharmacists*
Patient factor/ type of illness	6
Quality of generics/ excipients	5
Manufacturer's reputation	2

representatives for educational material. While these two sources were important to physicians as sources of credible information, consultation with other physicians was also a major factor (Table 2). Since a manufacturer's reputation influences the confidence of professionals, manufacturers of generic products should consider providing more evidence demonstrating therapeutic equivalence of their products.

A positive role for pharmacovigilance

Pharmacovigilance can also have a significant impact on increasing confidence in the therapeutic equivalence in generics. Through active pharmacovigilance, medicines (both generic and innovator) associated with therapeutic failure or adverse effects could be better monitored for potential problems. Currently, the Ministry of Health relies on the spontaneous reporting method, Pharm-

Table 2. Physicians and pharmacists: credibility of information sources

Information source	No. physicians (Total = 242) *	No. pharmacists (Total = 36)*
Medical Journals	66	12
Drug manufacturers/drug representatives	66	12
Physicians	64	0
Pharmacists	13	2
Ministry of Health	11	4
Internet	8	2

** Values in columns do not balance due to non-responders.*

watch, but the success of this method requires continuous oversight [10–12]. Programmes to encourage physicians, pharmacists, other health professionals and patients to submit reports of problems with drug therapy may need to be considered. Confidence in the programme can be further reinforced by ensuring that appropriate action is taken in response to all reports.

It is important to recognize that doubts in generic substitutability reflected in this survey are similar to those reported over ten years ago [8] and therefore consideration should be given to more proactive methods of pharmacovigilance. Action must be taken to ensure that offering patients cheaper drugs does not translate into inferior therapy, thus compromising patient healthcare.

The authors wish to thank the Jamaica Fair Trading Commission and The Consumers Affairs Commission for their collaboration in the surveys.

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Frequently asked questions about generic medicines

In Australia, generic products must be bioequivalent to the innovator brand name product, or the market leader, before they are approved. Australia has rigorous scientifically based evaluation procedures for generic medicines based on the internationally accepted principle of bioequivalence. Under the Pharmaceutical Benefits Scheme, generic substitution is only permitted if two products are bioequivalent. Consumers should be encouraged to know and record the name of the active ingredient (International Nonproprietary Name) in the medicines they are receiving to avoid confusion between different brands of medicines. Healthcare professionals have a key role in helping consumers understand any real or perceived differences (or lack thereof) between different brands of medicines. Prescribing generics helps to contain health costs.

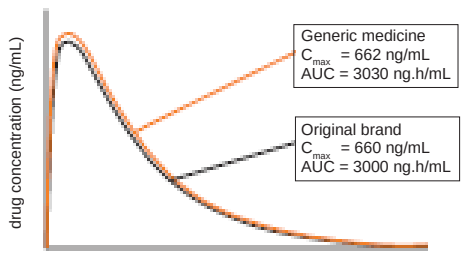
When the patent of an innovator drug expires, other manufacturers can make generic versions. A generic drug contains the same active ingredient as another product, but is marketed under a different name. In Australia, the Pharmaceutical Benefits Advisory Committee (PBAC) recognises the interchangeability of different brands containing the same active ingredient, providing these brands are proven to be bioequivalent (1–4).

What is bioequivalence?

Two products are bioequivalent when they produce such similar plasma concentrations of the active ingredient that their clinical effects can be expected to be the same. In a standard bioequivalence test both products are administered on separate occasions to healthy volunteers. Bioequivalence is then determined by comparing the peak plasma concentration (Cmax), time to achieve a maximal concentration (Tmax) and the extent of absorption (area under the concentration-time curve, AUC) of the products (Fig. 1).

Figure 1. Bioequivalence analysis – a hypothetical bioequivalence study

Mean concentration-time curves for two brands of a drug after single oral doses.



The original brand : generic medicine ratio for AUC is 0.99 (90% CI 0.91 to 1.04) and for C_{max} is 0.99% CI 0.92 to 1.07)

C_{max}	peak plasma concentration
AUC	area under the concentration-time curve
CI	confidence interval

Reprinted from NPS News, 2006;44-3.

These studies are well suited to identifying potentially significant differences in the delivery characteristics of the active substance of different products. The same bioequivalence principles apply to new drugs when different formulations of an active ingredient are compared. Bioequivalent products are marked with a superscript a or b in the Schedule of Pharmaceutical Benefits (5).

Is bioequivalence clinically important?

Yes, only those products that have been proven to be bioequivalent should be used interchangeably. On scientific grounds there

is no reason to be concerned about substituting a generic product for a branded product that is flagged as being bioequivalent (5). Switching inequivalent products may lead to lower or higher blood concentrations of a drug in a patient. This may increase the risk of therapeutic failure or drug-related toxicity.

The precise extent to which inequivalence between two formulations will affect the clinical response depends on their pharmacological and/or therapeutic properties. It depends specifically on which part of the drug concentration-effect curve is affected by any concentration difference (4). For example, if the drug is usually dosed close to the upper flat part of the dose response curve, then large changes in plasma concentration will result in only small changes in therapeutic response or adverse effects. Theoretically, this is a greater concern for drugs with a narrow therapeutic index, such as carbamazepine, digoxin and sodium valproate. However, this is not as problematic as may be predicted because patients taking these drugs are generally closely monitored (either by measuring concentrations or effects). For drugs with wider safety margins, there should be no concerns about a change in response when switching from one bioequivalent brand to another.

Which medicines should not be substituted?

Products that are not bioequivalent should not be substituted for each other. For example, metoprolol is available as both an intermediate release and a modified release tablet. These dose forms are not bioequivalent and should not be substituted. There are two innovator brands of warfarin available in Australia. These have not been proven to be bioequivalent and so it is recommended that warfarin products should not be substituted.

There has been considerable debate regarding the bioequivalence of drugs with a narrow therapeutic index, that is, drugs for which a small change in blood drug concentration leads to significant change in therapeutic response or toxicity (6).

These drugs generally display relatively minor variability within a patient from day to day but often display considerable variability between patients (4,6). Taken together this implies that the dose required to achieve the same concentration in the body, and therefore the same pharmacological effect, might be quite different between different patients. However, within a patient the dose requirements are unlikely to vary greatly over time and between doses while the patient is clinically stable. Bioequivalence principles and criteria equally apply to medicines with a narrow safety margin (6,7).

Can people have a reaction to the excipients in different products?

Yes, although adverse reactions to excipients are rare. Pharmaceutical products contain the active pharmacological ingredient and a range of excipients that are designed to deliver the active drug optimally in a reliable and reproducible manner. These excipients can be diluents, binders, fillers, surfactants, lubricants, coatings and dyes. Excipients are generally considered ‘inactive’, but there is some evidence to suggest that excipients can have an impact on patient tolerability (8). The main risk is allergy or intolerance to a specific ingredient such as lactose. The range of excipients used pharmaceutically is small, and the type used in individual products must be carefully chosen so that bioequivalence is achieved. The quality and safety of all excipients are carefully reviewed by the Therapeutic Goods Administration (TGA) and excipients can only be used if they are safe and non-toxic. It may not be

possible to determine which ingredients in either generic or branded products may cause an allergic reaction given that formulations are likely to be similar. Patients who are aware of their allergies can refer to the ingredients listed in the Consumer Medicines Information that accompanies the product.

How can patients avoid being confused by the brand name of generic products?

Patients should be encouraged to know and record the name of the active ingredient in the medicine they are taking rather than the product brand name. In this way a patient will understand that the same medicine may be available in different brands. This has implications for the way medicines are labelled. Ideally, the active ingredient in the product should be displayed with greater or equal prominence to the brand name on the packaging as recommended by the TGA in the 'Best practice guideline on prescription medicine labelling' (9).

Public hospitals are likely to only have one or two brands of a medicine and these are often generic products. As patients move in and out of hospital it is likely that generic substitution will occur to a greater extent. This reinforces the need for patients to be aware of and carry a list of the name of the active ingredient or generic name of their medicines to maintain effective management of their condition (10).

When deciding whether to substitute a generic product for a branded product, one must always consider the patient's understanding of their medicines and the risk of medication misadventure. Discuss this with the patient and provide appropriate information (3). If there is potential for confusion on the part of the patient and there is a risk of dose duplication, then generic substitution may need to be avoided (independent of the drug involved) unless the patient or carer fully understands the difference between the various brands of the same medicine. Clearly elderly patients, those with cognitive impairment and patients taking multiple medicines for serious chronic illness are at greatest risk of misadventure from their drugs.

Do community pharmacists make a bigger profit if they substitute a generic drug?

Not necessarily. Under the Brand Premium Policy of the Pharmaceutical Benefits Scheme (PBS), pharmacists are allowed to substitute a generic product when a branded product is prescribed, unless the prescriber directs otherwise. The PBS provides a subsidy up to the price of the cheapest brand of a drug in a particular therapeutic area. This often creates a price difference between generic and branded products.

The pharmacist's profit margin varies from drug to drug and product to product. In the past, cost savings for community pharmacists arose when they purchased bulk orders of generic drugs directly from manufacturers. This issue was not unique to generic products because some manufacturers of branded medicines also sold their products directly to community pharmacies under price-volume agreements. This is one of the many economic issues that community pharmacists have to deal with in the efficient running of their businesses. Recent PBS reforms have created different remuneration schedules for generic and branded medicines resulting in these cost savings now being retained within the PBS.

Can the bioavailability of bioequivalent products differ?

For two drugs to be bioequivalent, the 90% confidence intervals (90% CI) for the ratio of each pharmacokinetic parameter, C_{max} and AUC, must lie within the range 0.8–1.25 (sometimes also expressed as 80–125%).

The 90% CI of 0.8–1.25 is a numerical index and not a direct measure of the difference in systemic concentrations of the active ingredient resulting from administration of the two products. It does not mean that the Cmax and AUC ratios estimated for each formulation can vary by –20 to +25%. In reality, for a product to fit within these relatively tight confidence limits the mean AUC and Cmax must be very close, and any difference in bioavailability is certainly less than 10% (4).

Conclusion

Bioequivalence criteria used in Australia have been defined and refined over many years and are internationally recognised as the acceptable criteria for assessing bioequivalence (1). There is persuasive evidence that the current internationally accepted limits and approaches to bioequivalence can accommodate all medicines (6,7).

Only drugs that are marked as bioequivalent should be substituted for each other. Likewise, drugs that are not bioequivalent should not be exchanged. To avoid confusion, healthcare professionals should, where possible, reinforce the name of the active ingredient in the medicine, when prescribing, dispensing and administering medicines to patients.

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Quality Assurance Update

Latest developments in ICH Quality

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) recently convened a Quality Satellite Roundtable at Rockville, Maryland, USA. During the Satellite, the Quality Informal Implementation Working Group (IWG) met from 27 to 28 September 2007.

ICH-Q8(R1): Pharmaceutical Development Revisited

The ICH Steering Committee (SC) endorsed the development of a new guideline in October 2003 that would describe the harmonized contents of Section 3.2.P.2. "Pharmaceutical Development" within the Quality Module of the Common Technical Document (CTD).

The final draft of the document Q8 – Pharmaceutical development (Part 1 - core guideline) was recommended for adoption to the regulatory bodies of the European Union, Japan and USA in November 2005. The SC authorized the preparation of Part 2, which is an addendum to ICH Q8 Pharmaceutical development and provides further clarification of key concepts outlined in the core guideline. The SC released the document ICH-Q8(R1): Pharmaceutical Development for public consultation in Yokohama in November 2007. The structure of the document is outlined and arbitrarily selected passages are excerpted, as follows.

Approaches to pharmaceutical development

The theme of this section is described in table 1 overleaf, which illustrates some potential contrasts between a minimal

The six members of ICH:

- European Commission of the European Union
- European Federation of Pharmaceutical Industries and Associations
- Japan Pharmaceutical Manufacturers Association
- Ministry of Health, Labor and Welfare, Japan
- Pharmaceutical research and Manufacturers of America
- US Food and Drug Administration

Non-voting observers serving as a link between ICH and non-ICH countries and regions are:

- European Free Trade Association
- Health Canada
- International Federation of Pharmaceutical Manufacturers and Associations
- World Health Organization

Table 1: Approaches to pharmaceutical development

Aspect	Minimal approach	Enhanced, quality by design approach
Overall pharmaceutical development	• Mainly empirical • Developmental research often conducted one variable at a time	• Systematic, mechanistic understanding of input material attributes and process parameters to drug product CQAs • Multivariate experiments to understand product and process • Establishment of design space • PAT tools utilized
Manufacturing process	• Fixed • Validation primarily based on initial full-scale batches • Focus on optimization and reproducibility	• Adjustable within design space • Lifecycle approach to validation and, ideally, continuous process verification • Focus on control strategy and robustness • Use of statistical process control methods
Process controls	• In-process tests primarily for • go/no go decisions • Off-line analysis	• PAT tools utilized with appropriate feed forward and feedback controls • Process operations tracked and trended to support continual improvement efforts post-approval
Product specification	• Primary means of control * Based on batch data available at time of registration	• Part of the overall quality control strategy • Based on desired product performance with relevant supportive data
Control Strategy	• Drug product quality controlled primarily by intermediate and end product testing.	• Drug product quality ensured by risk-based control strategy for well understood product and process • Quality controls shifted upstream, with the possibility of real-time release or reduced end-product testing
Lifecycle Management	• Reactive (i.e., problem solving and corrective action)	• Preventive action • Continual improvement facilitated

approach and an enhanced approach regarding different aspects of pharmaceutical development and lifecycle management. Current practices in the pharmaceutical industry vary and typically lie between these approaches.

The EWG concluded that pharmaceutical development should include, at a minimum, the following elements:

- Defining the target product profile as it relates to quality, safety and efficacy, considering e.g., the route of administration, dosage form, bioavailability, dosage, and stability
- Identifying critical quality attributes (CQAs) of the drug product, so that those product characteristics having an impact on product quality can be studied and controlled
- Determining the quality attributes of the drug substance, excipients etc., and selecting the type and amount of excipients to deliver drug product of the desired quality
- Selecting an appropriate manufacturing process
- Identifying a control strategy.

A more systematic approach could facilitate continual improvement and innovation throughout the product lifecycle (See ICH Q10 *Pharmaceutical Quality System*).

Elements of pharmaceutical development

Target product profile. A target product profile is a prospective summary of the quality characteristics of a new drug product that ideally will be achieved by the time of submitting an application for marketing authorization.

Critical quality attributes. A critical quality attribute (CQA) is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. CQAs are generally associated with the drug substance, excipients, intermediates, and drug product.

Linking material attributes and process parameters to CQAs. Risk assessment tools can be used to identify and rank parameters (e.g., operational, equipment, input material) with potential to have an impact on product quality based on prior knowledge and initial experimental data.

Design space. The linkage between the process inputs (input variables and process parameters) and the critical quality attributes can be described in the design space.

Selection of variables. All variables and their ranges within which consistent quality can be achieved should be selected for inclusion in the design space.

Defining and describing a design space in a submission. An example of a design space presentation (excerpted from the document) is set out in Figure 1. Design space is determined from the common region of successful operating ranges for multiple CQAs. The relations of two CQAs, i.e., friability and dissolution, to two process parameters of a granulation operation are shown in Figures 1a and 1b. Figure 1c shows the overlap of these regions and the maximum ranges of the potential design space.

Unit operation design space(s). The applicant can choose to establish independent design spaces for one or more unit operations, or to establish a single design space that spans multiple operations

Relationship of design space to scale and equipment. If the applicant wishes the design space to be applicable to multiple operational scales, the design space

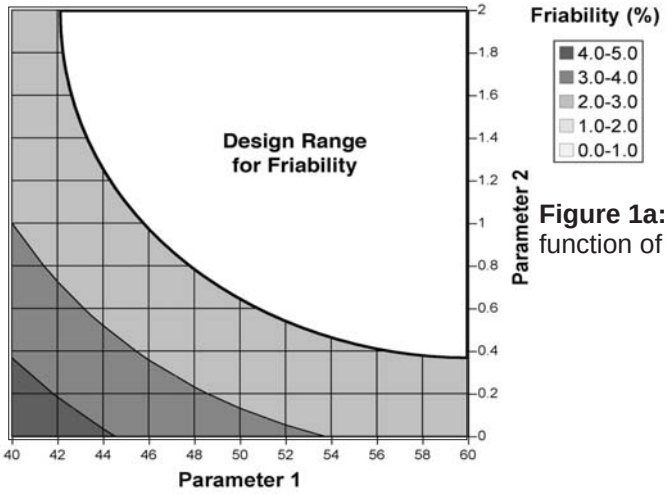


Figure 1a: Contour plot of friability as a function of Parameters 1 and 2. Figure

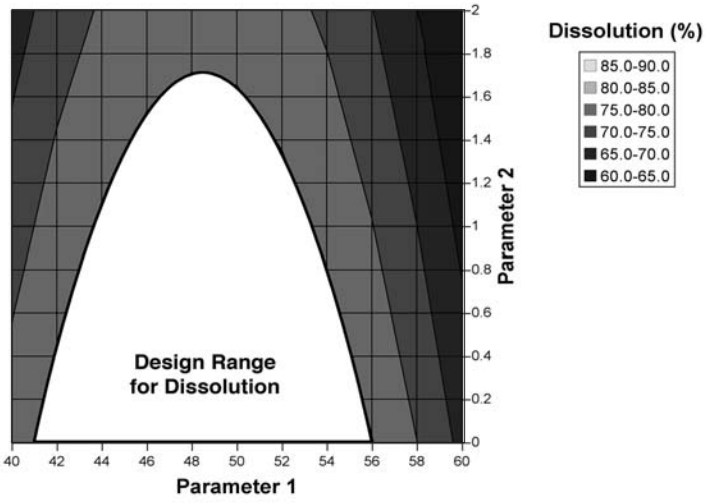


Figure 1b: Contour plot of dissolution as a function of Parameters 1 and 2.

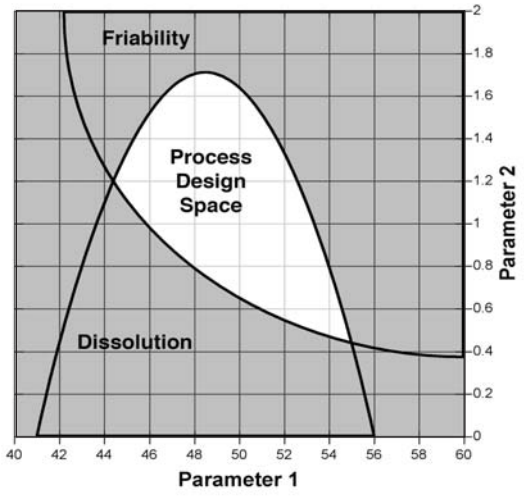


Figure 1c: Potential process design space, comprised of the overlap region of design ranges for friability and or dissolution.

should be described in terms of relevant scale-independent parameters.

Design space versus proven acceptable ranges. A combination of proven acceptable ranges does not constitute a design space. (See Figures 1a and 1b.)

Design space and edge of failure. It can be helpful to know where edges of failure could be, or to determine potential failure modes. However, it is not an essential part of establishing a design space.

Control strategy. The elements of the control strategy discussed in Section P.2 of the dossier should describe and justify how in-process controls and the controls of input materials (drug substance and excipients), container closure system, intermediates and end products contribute to the final product quality. These controls should be based on product, formulation and process understanding and should include, at a minimum, control of the critical parameters and attributes.

Product lifecycle management and continual improvement. Throughout the product lifecycle, companies have opportunities to evaluate innovative approaches to improve product quality (see ICH Q10).

Submission of pharmaceutical development and related information in Common Technical Document (CTD) format

Pharmaceutical development information is submitted in Section P.2 of the CTD.

Quality Risk Management and Product and Process Development. Risk analyses linking the design of the manufacturing process to product quality can be included in P.2.3.

Design Space. The product and manufacturing process development sections of the application (P.2.1, P.2.2, and P.2.3) are appropriate places to summarize and describe product and process development studies that provide the basis for the design space(s).

Control Strategy. The section of the application that includes the justification of the drug product specification (P.5.6) is a good place to summarize the control strategy.

Drug Substance Related Information. If drug substance CQAs have the potential to affect the CQAs or manufacturing process of the drug product, some discussion of drug substance CQAs can be appropriate in the pharmaceutical development section of the application (e.g., P.2.1).

What's next for ICH Q8?

Comments will be delivered to the ICH meeting in fall 2008 to be considered for incorporation into the Step 2 draft. Step 2 of the ICH process is reached when the ICH Steering Committee agrees, based on the report of the Expert Working Committee, that there is sufficient scientific consensus on the technical issues for the draft guideline or recommendation to proceed to the next stage of regulatory consultation or Step 3. The next step is Step 4 or adoption of the ICH guideline. Step 4 is reached when the ICH Steering Committee agrees, on the basis of the report from the regulatory Rapporteur of the Expert Working Group, that there is sufficient scientific consensus on the technical issues. Step 4 is followed by Step 5 or implementation.

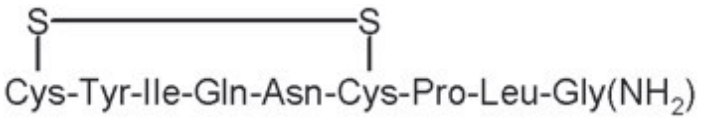
The ICH Quality Satellite Roundtable meeting held in Rockville, Washington concluded that the principles of Q8, Q9, and Q10 are applicable to chemical and biotech drug substances and drug products. The Quality Informal Implementation Working Group (IWG) in Yokohama proposed and the Steering Committee agreed to the establishment of a common formal IWG to ensure globally consistent implementation of Q8, Q9 and Q10. The formal IWG will start work in June 2008.

Consultation Documents

International Pharmacopoeia

OXYTOCINUM
OXYTOCIN

Draft proposal for the *International Pharmocopoeia* (September 2007). Please address any comments to Quality Assurance and Safety: Medicines, PSM, World Health Organization, 1211 Geneva 27, Switzerand. Fax +4122791 4730 or e-mail to rabhouansm@who.int



$C_{43}H_{66}N_{12}O_{12}S_2$

Relative molecular mass. 1007

Chemical name. L-Cysteinyl-L-tyrosyl-L-isoleucyl-L-glutamyl-L-asparaginyl-L-cysteinyl-L-prolyl-L-leucylglycinamide cyclic (1!6)-disulfide; CAS Reg. No. 50-56-6.

Other name. Alpha-hypophamine.

Description. White or almost white powder.

Solubility. Very soluble in water. It dissolves in dilute solutions of acetic acid and of ethanol.

Category. Uterine-stimulating (Oxytocic).

Storage. Oxytocin should be kept in an airtight container, protected from light, at a temperature of 2 °C to 8 °C. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

Labelling. The designation on the container should state the oxytocin peptide content ($C_{43}H_{66}N_{12}O_{12}S_2$).

Additional information. Oxytocin is hygroscopic.

Requirements

Definition. Oxytocin is a synthetic cyclic nonpeptide having the structure of the hormone produced by the posterior lobe of the pituitary gland that stimulates contraction of the uterus and milk ejection in receptive mammals. It is available in the freeze-dried form as an acetate.

Oxytocin contains not less than 93.0% and not more than 102.0% of $C_{43}H_{66}N_{12}O_{12}S_2$, calculated with reference to the anhydrous and acetic acid-free substance.

By convention, for the purpose of labelling oxytocin preparations, 1 mg of oxytocin peptide ($C_{43}H_{66}N_{12}O_{12}S_2$) is equivalent to 600 IU of biological activity.

Identity tests

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

A. Examine the chromatograms obtained in the assay. The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with the reference solution.

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

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

C.1 Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 70 volumes of dichloromethane R, 30 volumes of methanol R, 6 volumes of purified water and 1 volume of glacial acetic acid R as the mobile phase. Apply separately to the plate 10 ìl of each of 2 solutions in methanol containing (A) 5 mg of the test substance per ml and (B) 5 mg of oxytocin RS per ml. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in a current of cool air. Examine the chromatogram in ultraviolet light (254 nm).

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

C.2 Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R5 as the coating substance and a mixture of 70 volumes of dichloromethane R, 30 volumes of methanol R, 6 volumes of purified water and 1 volume of glacial acetic acid R as the mobile phase. Apply separately to the plate 10 ìl of each of 2 solutions in methanol containing (A) 5 mg of the test substance per ml and (B) 5 mg of oxytocin RS per ml. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in a current of cool air. Spray with ninhydrin. Heat the plate for a few minutes at 120 ˚C. Examine the chromatogram in daylight.

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

D. The absorption spectrum of a 0.30 mg/ml solution, when observed between 240 nm and 330 nm, exhibits a maximum at about 275 nm; the specific absorbance ($A_{1cm}^{1\%}$) is 14 to 16, calculated with reference to the anhydrous and acetic acid-free substance.

Specific optical rotation. Use a 5.0 mg/ml solution and calculate with reference to the anhydrous and acetic acid-free substance; $[\alpha]_D^{20\,^\circ C}$ = -24.0˚ to -28.0˚.

pH value. pH of a 20 mg/ml solution in carbon-dioxide-free water R, 3.0-6.0.

Water. Determine as described under 2.8 Determination of water by the Karl Fischer method, Method A, using about 0.10 g of the substance; the water content is not more than 50 mg/g.

Acetic acid content. Determine by 1.14.4 High performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with octadecylsilyl silica gel for chromatography R (5 ìm).

Use the following conditions for gradient elution:

Mobile phase A: Dilute 0.7 ml of phosphoric acid (~1440 g/l) TS with 900 ml purified water; adjust the pH to 3.0 with sodium hydroxide (~200 g/l) TS and dilute to 1000 ml with purified water.

Mobile phase B: Methanol R.

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0 – 5	95	5	Isocratic
5 – 10	95 to 50	5 to 50	Linear gradient
10 – 20	50	50	Isocratic
20 – 22	50 to 95	50 to 5	Linear gradient
22 – 30	95	5	Isocratic re-equilibration

Prepare the following solutions:

For solution (1), dissolve 15.0 mg of the substance to be examined in a mixture of 5 volumes of mobile phase B and 95 volumes of mobile phase A and dilute to 10.0 ml with the same mixture of mobile phases.

For solution (2), prepare a 0.10 g/l solution of glacial acetic acid R in a mixture of 5 volumes of mobile phase B and 95 volumes of mobile phase A.

Operate with a flow rate of 1.2 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 210 nm.

Inject alternatively 10 µl each of solutions (1) and (2). In the chromatograms obtained, the peak corresponding to acetic acid has a retention time of 3-4 min. The baseline presents a steep rise after the start of the linear gradient, which corresponds to the elution of oxytocin from the column. Calculate the acetic acid content; not less than 60 mg/g and not more than 100 mg/g.

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

Use the following conditions for gradient elution:

Mobile phase A: 15 volumes of acetonitrile R, 15 volumes of phosphate buffer and 70 volumes of purified water.

Mobile phase B: 70 volumes of acetonitrile R, 15 volumes of phosphate buffer and 15 volumes of purified water.

Prepare the phosphate buffer by dissolving 31.2 g of sodium dihydrogen phosphate dihydrate R in 1000 ml of purified water.

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0 – 5	100	0	Isocratic
5 – 20	100 to 94	0 to 6	Linear gradient
20 – 50	94 to 60	6 to 40	Linear gradient
50 – 51	60 to 100	40 to 0	Linear gradient
51-65	100	0	Isocratic re-equilibration

Prepare the following solutions using mobile phase A as diluent. For solution (1) use 0.50 mg of the test substance per ml. For solution (2) dilute a suitable volume of solution (1) to obtain a concentration equivalent to 5.0 ìg of oxytocin per ml.

For the system suitability test: prepare solution (3) using 3 ml of solution (1) and 2 ml of sulfuric acid (10 g/l), heat carefully in a boiling water-bath for 20 minutes.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 220 nm.

Maintain the column temperature at 40 ˚C.

Inject 50 ìl of solution (3). The test is not valid unless the resolution between the peak due to oxytocin (retention time about 25 minutes) and the peak with a relative retention of about 0.9 is not less than 1.4.

Inject alternatively 50 µl each of solutions (1) and (2).

In the chromatogram obtained with solution (1), the area of any peak, other than the principal peak, is not greater than 1.5 times the area of the principal peak obtained with solution (2) (1.5%). The sum of the areas of all peaks, other than the principal peak, is not greater than 5.0 times the area of the principal peak obtained with solution (2) (5%). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Assay

Either method A or method B may be applied.

A. Determine by High performance liquid chromatography as described in the test for related substances with the following modifications.

Prepare solution (2) as follows. Dissolve the contents of a vial of oxytocin RS in mobile phase A to obtain a concentration of 0.50 mg/ml.

Inject alternatively 50 µl each of solutions (1) and (2).

Calculate the content of oxytocin ($C_{43}H_{66}N_{12}O_{12}S_2$) from the declared content of $C_{43}H_{66}N_{12}O_{12}S_2$ in oxytocin RS.

B. Dissolve about 30 mg, accurately weighed, in sufficient purified water to produce 100 ml. Measure the absorbance of this solution in a 1-cm layer at the maximum at about 275 nm, and calculate the content of $C_{43}H_{66}N_{12}O_{12}S_2$, using the absorptivity value of 1.49 ($A_{1cm}^{1\%} = 14.9$).

Additional requirement for Oxytocin for parenteral use
Complies with the monograph "Parenteral preparations".

Bacterial endotoxins. Carry out the test as described under 3.4 Test for bacterial endotoxins; contains not more than 300 IU of endotoxin RS per mg.

OXYTOCINUM INJECTIO
OXYTOCIN INJECTION

Draft proposal for the *International Pharmocopoeia* (October 2007). Please address any comments to Quality Assurance and Safety: Medicines, Medicines Policy and Standards, World Health Organization, 1211 Geneva 27, Switzerand. Fax +4122791 4730 or e-mail to rabhouansm@who.int

Description. A clear, colourless liquid.

Category. Uterine-stimulating (Oxytocic).

Storage. Oxytocin injection should be kept protected from light and stored at a temperature between 2 °C and 8 °C.

Labelling. The designation on the container should state the content in IU per ml and the oxytocin peptide ($C_{43}H_{66}N_{12}O_{12}S_2$) content in mg per ml. It should also state animal source if naturally derived, or state that it is synthetic.

Additional information. Strength in the current WHO Model list of essential medicines: 10 IU per ml in 1-ml ampoule.

Oxytocin injection is normally intended for intravenous or intramuscular administration.

REQUIREMENTS

Oxytocin injection complies with the monograph for "Parenteral preparations".

Definition. Oxytocin injection is a sterile solution of Oxytocin in a suitable diluent. Oxytocin injection contains not less than **90.0%** and not more than **110.0%** of the amount of the peptide $C_{43}H_{66}N_{12}O_{12}S_2$ stated on the label.

Identity tests

Either test A or test B may be applied.

A. Examine the chromatograms obtained in the assay. The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with the reference solution.

B. Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R5 as the coating substance and a mixture of 70 volumes of dichloromethane

R, 30 volumes of methanol R, 6 volumes of purified water and 1 volume of glacial acetic acid R as the mobile phase. Apply separately to the plate 20 ìl of each of the following two solutions. For solution (A) evaporate 10.0 ml of oxytocin injection to dryness at 30 ˚C under reduced pressure (not exceeding 0.6 kPa or 5 mm of mercury) and dissolve the residue in 1.0 ml of methanol R. Prepare solution (B) in methanol R containing 165.0 µg/ml of oxytocin RS. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in a current of cool air. Stain the plate with iodine vapour and examine in daylight.

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

pH value. pH of the injection, 3.0–5.0.

Assay

Determine by 1.14.4 High performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with octadecylsilyl silica gel for chromatography R (5 ìm).

Use the following conditions for gradient elution:

Mobile phase A: 15 volumes of acetonitrile R, 15 volumes of phosphate buffer and 70 volumes of purified water.

Mobile phase B: 70 volumes of acetonitrile R, 15 volumes of phosphate buffer and 15 volumes of purified water.

Prepare the phosphate buffer by dissolving 31.2 g of sodium dihydrogen phosphate dihydrate R in 1000 ml of purified water.

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0 – 5	100	0	Isocratic
5 – 20	100 to 94	0 to 6	Linear gradient
20 – 50	94 to 60	6 to 40	Linear gradient
50 – 51	60 to 100	40 to 0	Linear gradient
51 - 65	100	0	Isocratic re-equilibration

Use the following solutions.

For solution (1) use undiluted injection. For solution (2) dissolve the contents of vial of oxytocin RS in mobile phase A to obtain a concentration of 16.7 µg/ml.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 220 nm.

Maintain the column temperature at 40 ˚C.

Inject alternatively 50 µl each of solutions (1) and (2).

Calculate the content of oxytocin ($C_{43}H_{66}N_{12}O_{12}S_2$) from the declared content of $C_{43}H_{66}N_{12}O_{12}S_2$ in oxytocin RS.

Recent Publications, Information and Events

GMP for herbal medicines

The safety and quality of herbal materials and finished herbal products have become a major concern for health authorities. Requirements and methods for quality control of finished herbal products are far more complex than for chemical drugs. The quality of the finished herbal product is also influenced by the quality of the raw materials used. The manufacturing process is one of the key steps where quality control is measured and good manufacturing process (GMP) is the most efficient tool.

Since GMP control for herbal medicines needs to meet technical requirements for both herbal and chemical drugs, the *WHO Guideline on good manufacturing practices (GMP) for herbal medicines* combines the two sets of guidelines in one publication.

Reference: World Health Organization. *WHO Guideline on good manufacturing practices (GMP) for herbal medicines.* Available from: bookorders@who.int or http://www.who.int/medicines

Quality of antiretrovirals in African countries

In 2006, almost two-thirds of persons infected with HIV were living in Sub-Saharan Africa. Provision of antiretroviral treatment by both public and private sector facilities has increased tenfold between December 2003 and June 2006.

The first requirement of any treatment programme is the availability of antiretrovirals of acceptable quality, safety and efficacy. Antiretrovirals manufactured below established standards of quality can lead to therapeutic failure, development of drug resistance and toxic or adverse reactions.

A survey of the quality of antiretroviral medicines circulating in selected African countries was carried out by WHO in collaboration with the national drug regulatory authorities of Cameroon, the Democratic Republic of Congo, Kenya, Nigeria, United Republic of Tanzania, Uganda and Zambia.

Reference: World health Organization. *A survey of the quality of antiretroviral medicines circulating in selected African countries.* Available from prequallaboratories@who.int or http:www.who.int/medicines

The Health Journey

The Health Journey is a simple and useful participatory methodology for understanding the experiences of people living with HIV in trying to access and use health and other support services. It provides a starting point for planning and monitoring community engagement and provision of community-centred health and support services. It is intended for individuals, groups and organizations working in HIV care and support, but it can easily be adapted to other issues both within and beyond the HIV field.

Outcomes from the methodology have already contributed to improved coordination of community support and health care for people with HIV and to reduction of stigma and discrimination in a variety of settings, within the Caribbean, Zambia, Uganda, Myanmar and China.

Part 1 of the health journey explains what a health journey is and who can make use of the methodology;

Part 2 explains: how to set up and use the methodology; and

Part 3 provides: five different examples of health journey workshops, what impacts resulted from them and a list of useful resources.

Reference: International HIV/AIDS Alliance. The Health Journey - Understanding the dimensions of care and treatment for people with HIV: a community-centred methodology. Printed copies are available from publications @aidsalliance.org and http://www.aidsalliance.org

Human rights guidelines for pharmaceutical companies

The UN Special Rapporteur on the right of everyone to the enjoyment of the highest attainable standard of physical and mental health, has launched for public consultation draft Human Rights Guidelines for Pharmaceutical Companies in relation to Access to Medicines.

Access to medicines is a central feature of the right to the highest attainable standard of health. States have primary responsibility for enhancing access to medicines, as set out in the expert's report to the UN General Assembly last year (13 September 2006, A/61/338). The Special Rapporteur routinely questions Governments about their national medicines policies and implementation plans.

Pharmaceutical companies have a profound impact - both positive and negative - on Governments' ability to realise the right to the highest attainable standard of health. It is time to identify what pharmaceutical companies should do to help realize the human right to medicine.

Reference: Draft Guidelines, and other initiatives of the Special Rapporteur at www2.essex.ac.uk/human_rights_ centre/rth/ and http://www.ohchr.org/english/issues/health/right/index.htm

ARV price report from WHO

The new summary report by the WHO/AMDS Global Price Reporting Mechanism (GPRM) confirms that median prices of the most commonly prescribed antiretroviral medicines (ARVs) in fixed dose combination (stavudine 30 mg + lamivudine 150 mg + nevirapine 200 mg) continued to decline during the period from January to June 2007. They are now available for less than US$ 100 per patient per year (pppy) with a median price of US$ 77 in low-income countries and US$ 99 in middle-income countries.

The same trend is being observed with ARVs for children. However, the costs of oral solutions for infants/young children still remain high. For instance, the median cost of the most widely prescribed regimen as oral solution (zidovudine 10 mg/ml + lamivudine 10 mg/ml + nevirapine 10 mg/ml) for a five kg infant is now US$ 174 (pppy) in low-income countries and US$ 235 (pppy) in middle-income countries.

Reference: World Health Organization. AMDS summary Report at http://www.who.int/hiv/amds/GPRMsummaryJuly2007.pdf