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Regulatory Challenges

Medical device regulation: a model framework

The term “medical devices” covers a vast array of products from simple tongue depressors to magnetic resonance equipment. The intended primary mode of action of a medical device on the human body, in contrast with that of medical products, is not metabolic, immunological or pharmacological although it may be assisted in its function by such means. With around one and a half million different devices available, it is one of the fastest growing markets today. As a consequence, the regulatory approval and licensing of medical devices is becoming more and more challenging.

Ensuring the availability of quality medicines and health care products begins with effective management at national level. National medicines regulatory authorities operate with varying success in many countries and aim to achieve effective regulation of medicines. The responsibilities of regulatory authorities are broad and activities may include licensing and control of manufacture, import, export, sale, distribution, promotion and advertising; supervision and control of clinical trials; assessing safety, efficacy and quality; conducting post-marketing surveillance and monitoring adverse events; inspecting manufacturers, importers, wholesalers and dispensers at regular intervals, and providing unbiased information to professionals and the public.

Curiously, medical devices have not received the same attention as medicines despite the significant investment that their purchase may represent for health care systems and the need to ensure safety, quality standard conformity and performance. This is partly because medical devices are frequently perceived as a procurement issue as opposed to an integral part of public health policy. Few developing countries have an authority with discrete responsibility for the management of medical devices. Unfortunately, lack of effective regulation may lead to the import of substandard devices or illegal re-processing and re-packaging of products.

In 2003, WHO addressed this issue through two projects geared to strengthen the ability of national authorities to manage medical devices.

Strengthening national regulatory authorities for medical devices

The first initiative was to expand the existing WHO tool developed to assess medicines regulatory authorities to include medical devices (1). The expanded tool was used in the People’s Republic of China in September 2003 to carry out a comprehensive review of the national systems used to regulate vaccines and medicines and medical devices. This was the first time that WHO had organized such a joint assessment and the harmonized approach was appreciated by the national health authorities and local WHO staff.

In carrying out the medical device assessment, six broad areas were identified, namely:

- Medical device regulatory systems
- Marketing authorization
- Postmarketing surveillance
- Test laboratories
- Quality systems auditing
- Clinical trials.

These assessments form the basis of an institutional development plan, including training needs, and follow-up support. They are particularly useful in identifying areas for improvement. For example, it is estimated that some costly and time-consuming procedures could be avoided by the adoption of existing international standards for medical devices. The joint assessment tool and follow-up plans are now being refined and will be applied in other countries.

Harmonization of medical device regulations

The Global Harmonization Task Force (http://www.ghtf.org) was set up in 1993 by the five major global device producing and regulatory bodies — Australia, Canada, the European Union, Japan and the United States of America — with a view to harmonizing standards and regulatory practices across countries. The objective is to reduce regulatory barriers, facilitate trade and

improve access to safe, effective technologies. Much progress has been made towards this objective over the last decade yet developing countries, who import around 90% of the medical devices they need, remain marginalized in this process, largely because of lack of access to knowledge and best practice guidelines.

The recent WHO publication *Medical Device Regulations: Global Overview and Guiding Principles* (1) aims to bridge this gap. It provides a matrix of the entire life cycle of a medical device – from conception to disposal – and the policies that should be in place to manage each stage in this life cycle. Priorities are recommended for countries with limited infrastructure or resources, with suggestions on how to build towards a more effective system. The major issues covered in the publication are summarized as follows.

Safety: The safety of the patient – and indeed of the user and the community – is a priority for governments in authorizing the sale of a medical device. A medical device must provide benefit for the patient. Potential hazards need to be weighed against the gain. Devices are therefore classified according to the potential risks, and the higher the risk the more stringent the controls. All active devices intended to administer or remove medicines, body liquids or other substances to or from the body are classified as low to moderate risk (e.g. hypodermic syringes or anaesthesia equipment). Devices incorporating a medicinal product that is liable to act on the human body with action ancillary to the device is in the highest risk category (e.g. heparin-coated catheters or wound dressings incorporating antimicrobial agents).

Stages of regulatory control: the three main stages of regulatory control are:

- pre-market: To ensure that the product to be sold meets standards of safety and performance;
- on-market: To ensure that the product is accurately labelled and advertised; and
- post-marketing: To ensure the continued safety and effectiveness of the product in use.

For *pre-market* regulations, governments with limited resources are advised to take advantage of existing approval systems and international standards rather than setting up demanding and costly pre-market regulations. During the introduction of the product *on-market*, priority should go to ensuring a system for registering the vendor and the device, which is essential for alerts or product recalls during the *post-marketing* surveillance phase.

International standards: all medical devices should meet a recognized international standard for quality and safety. An understanding of the different standard-setting systems, the processes used to develop standards, and their use in conformity assessment is essential for the establishment of medical device regulations. This is no mean task, since there are many types of standards that govern products, processes and services. *The WHO Medical Device Regulations* explain the purpose of prescriptive, design, performance and management specifications and standards of the International Standards Organization (ISO) specifically relating to medical devices. A grasp of the difference between voluntary or mandatory standards and current trends in their use is all the more important since the introduction of a new quality system for medical devices in 2003 (2).

Priority activities: regulatory programmes can be developed in stages according to a country's needs and resources. However, a core programme, based on a clear policy and involving the government, manufacturers, vendors, users and the patient, should encompass:

- Essential basic legislation to empower governments to stop sale or withdraw unsafe products, and to penalize fraudulent advertising.
- Training of customs officials using the device acceptance criteria outlined in the national policy to prevent substandard devices from entering the country.
- An information network to encourage the voluntary sharing of information, e.g. to prevent the recurrence of an adverse event or to investigate a potential hazard. The next step will involve adherence to a larger, international network for complaints and sharing of alerts.
- An inventory of devices and approved suppliers. It is the responsibility of the vendor to keep distribution records so that all similar products may be identified in case of need.
- Adoption of an internationally recognized medical device nomenclature system to enable accurate tracking and comparison.

WHO supports the efforts of the Global Harmonization Task Force towards global convergence of regulatory requirements. WHO is also keen to develop a uniform certification process for medical devices based on the principles of the WHO Model Certification Scheme on the Quality of Pharmaceutical Products (3), as well as an international vigilance agency to increase the safety of devices in use.

Guiding principles to ensure injection device security

Injections are the most common health care procedure worldwide. Best infection control practices for intradermal, subcutaneous and intramuscular injections recommend the use of a new, single use injection device for each injection and for the reconstitution of each unit of medication. Unsafe injection practices are avoidable but continue to place patients at risk. For example, 41% of all new hepatitis C virus infections in 2000 were transmitted through the reuse of injection devices without sterilization. WHO therefore requests all donors and lenders who finance injectable products to finance appropriate quantities of single use injection devices, single dose diluents, safety boxes and the cost of sharps waste management. All organizations involved in medicine donations are also urged to follow this recommendation (4).

Conclusion

There is no medical device regulatory system template that fits all. Some countries are large manufacturers of equipment and will need to focus on good manufacturing practice and comprehensive quality controls. Others may receive regular donations of equipment that will need to fall within a clear needs assessment policy, while many countries are currently in ongoing crisis situations and need special emergency assistance.

The two approaches outlined above – creating awareness of international best practices and providing WHO technical support to national regulatory authorities – are intended to address the need for medical device regulations at the national and global level (5).

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Safety and Efficacy Issues

Maternal use of SSRIs and neonatal effects

Maternal use of selective serotonin reuptake inhibitors (SSRIs) during or after pregnancy may result in adverse effects in newborn babies, due to a withdrawal effect following intra-uterine exposure, or a toxic effect from ingestion of an SSRI in breast-milk. The Australian Adverse Drug Reactions Advisory Committee (ADRAC) has received 26 reports of neonates with symptoms attributed to withdrawal effects due to maternal third trimester ingestion of SSRIs (paroxetine 10, sertraline 7, fluoxetine 7, citalopram 2). The table below presents the most frequently reported reactions. Other reactions included convulsions, tremor, fever and respiratory disorders (respiratory depression, apnoea, tachypnoea). Two babies had marked extensor posturing with back-arching. The usual day of onset, if reported, was the day of birth, but ranged from 0 to 4 days of age. The symptoms resolved in 2–3 days in most cases.

Frequent neonatal symptoms reported in association with maternal SSRI ingestion

Symptoms	Withdrawal syndrome	Breast-milk transfer
Agitation/Jitteriness	15	4
Poor feeding	7	4
Hypotonia	7	1
Sleepiness/Lethargy	0	3
Gastrointestinal symptoms	3*	3
Total reports	**26**	**13**

** In one case the symptoms may have been from breast-milk transfer.*

In addition, 13 reports have been received of neonatal adverse effects probably resulting from breast-milk transfer of an SSRI (sertraline 9, paroxetine 2, fluoxetine 2). There was some overlap of symptoms resulting from drug transfer into breast-milk and from drug withdrawal (see table above). However, sleepiness was reported only with breast-milk transfer, and in two cases the baby slept for prolonged periods.

One study found that 12 (22%) of 55 neonates exposed to maternal paroxetine in the third trimester required prolonged hospitalization for neonatal complications (1). The most common problem was respiratory distress (9 cases), but two neonates had hypoglycaemia and one each had bradycardia, tachycardia, jaundice and feeding problems. None had underlying pathology and all recovered following a brief period of intensive intervention. In the same study, exposure to paroxetine through breastfeeding caused symptoms in 8 (22%) of 36 infants, with alertness, sleepiness and irritability.

In adult users, withdrawal effects following paroxetine appear to be more likely than following use of other SSRIs, and hence neonatal withdrawal may be more likely with paroxetine, but this is yet to be demonstrated in comparative studies (2). However, paroxetine may have an advantage in breastfeeding since breast-milk transfer is proportionately lower than with fluoxetine or citalopram (3). One study in 11 infants detected sertraline in breast-milk but there were no adverse effects associated with exposure (4). It is probable that neonatal withdrawal effects would be minimized by using the lowest effective maternal dose, while breast-milk transfer can be treated by stopping or reducing the dose of SSRI, or by using milk formula.

Extracted from the Australian Adverse Drug Reactions Bulletin, Volume 22, Number 4, August 2003.

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ACE inhibitor, diuretic and NSAID: a dangerous combination

The control of hypertension by ACE inhibitors and diuretics and their beneficial effects in heart failure are antagonized by NSAIDs*. Concurrent use of NSAIDs and diuretics is associated with a twofold increase in the risk of hospitalization for heart failure compared with diuretics alone (1). Moreover, ACE inhibitors, NSAIDs and diuretics, individually or in combination, are involved in over 50% of cases of iatrogenic acute renal failure reported to the Australian Adverse Drug Reactions Advisory Committee (ADRAC).

More specifically, the combined use of ACE inhibitors, diuretics and NSAIDs, termed the "triple whammy", is implicated in a significant number of reports to ADRAC of drug-induced renal failure (2). This effect is also seen with COX-2 inhibitors and angiotensin receptor antagonists ("sartans") (3). In 2002, 28 of the 129 reports to ADRAC of acute renal failure implicated one of these combinations. Most reports to ADRAC of drug-induced renal failure relate to elderly patients, and this applies as well to renal failure associated with the triple therapy (median age 76 years). The fatality rate for ADRAC cases of renal failure with the "triple whammy" is 10%.

The use of ACE inhibitors and angiotensin receptor antagonists is increasing, as is the use of these agents in combination products with a diuretic. Episodes of renal failure appear to be precipitated by mild stress (e.g. diarrhoea, dehydration) in a patient taking the triple combination or by the addition of a third drug (usually an NSAID) to the stable use of the other two. ADRAC suspects that the risk of acute renal failure is underestimated and the syndrome underrecognized.

*Extracted from the Australian Adverse Drug Reactions Bulletin, Volume 22, Number 4, August 2003. * Ed. note. Referenced articles not mention use of acetylsalicylic acid as an NSAID.*

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Serious gastrointestinal effects with celecoxib and rofecoxib

The Australian Adverse Drug Reactions Advisory Committee (ADRAC) has received a significant number of reports of peptic ulcer (with and without perforation or haemorrhage) and of gastrointestinal (GI) haemorrhage with celecoxib (Celebrex®) and rofecoxib (Vioxx®).

Many of the patients with peptic ulcer had known risk factors: they were aged > 60 years (73% for celecoxib vs 97% for rofecoxib), they had a history of peptic ulcer (18% vs 0%) or they were taking other medication which increased their risk (45% vs 81%). However, 16 of those who developed peptic ulcer with celecoxib (none with rofecoxib) were aged < 60 years and had no stated risk factors. In five of these cases the ulcer was diagnosed within 4 weeks of initiation of celecoxib. In nine of the 16 cases, the diagnosis was confirmed by endoscopy, radiology, or during surgery.

Reports of peptic ulcer or GI haemorrhage with celecoxib and rofecoxib

	celecoxib	rofecoxib
PBS prescriptions May 2000 to Dec 2002	9.3 million	4.3 million
Total reports	3315	637
Total peptic ulcers	101	31
-with risk factors	84	31
-without risk factors	16	-
Total GI haemorrhage	250	56
-with risk factors	234	51
-without risk factors	16	5

Of the reports of GI haemorrhagic events (in the absence of a diagnosis of peptic ulcer), 16 cases with celecoxib and five with rofecoxib involved patients aged < 60 years, with no stated history of GI ulcer and no concurrent use of another NSAID. Those reports mentioning alcohol as a possible factor were excluded. For these 21 cases, time to

onset ranged from 1 day to 8 months (median 13 days). In four cases the reaction occurred after a single dose, and in one of these cases the patient's haematemesis recurred following a single dose a week later.

Initial results from clinical trials indicated a rate of upper GI ulceration with celecoxib or rofecoxib of around 2 per 100 patient-years during 6-9 months' treatment, significantly lower than with the nonselective NSAIDs (1, 2). However, while a pivotal study suggested that there may be a long-term advantage of rofecoxib over the nonselective NSAIDs for upper GI ulceration (1), results after 12 months' usage of celecoxib indicated similar rates of ulcer complications to diclofenac and ibuprofen (3). The differences between celecoxib and rofecoxib apparent in the ADRAC data may reflect the differences seen in the clinical trials and/or they may relate to differences between the populations of users. Whatever the absolute rates of peptic ulcer may be with celecoxib and rofecoxib, the serious events reported to ADRAC suggest that selective COX-2 inhibitors should be treated with similar caution to other NSAIDs.

Extracted from the Australian Adverse Drug Reactions Bulletin, Volume 22, Number 4, August 2003.

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Bisphosphonates and ocular disorders

Bisphosphonates inhibit bone resorption. Indications for their use vary according to the individual products, but they are used primarily to prevent or treat osteoporosis, Paget disease of bone, tumour-induced hypercalcaemia and conditions associated with increased osteoclast activity (predominantly lytic bone metastases and multiple myeloma). International data from spontaneous reporting systems for visual reactions associated with bisphosphonates suggest that, in rare instances, this class of medication can cause serious ocular adverse effects (1).

Pamidronate has been associated with ocular inflammation such as uveitis, nonspecific conjunctivitis, episcleritis and scleritis (1). Similar disorders have been linked to alendronate, clodronate, etidronate and risedronate (1–3). These ocular effects were initially thought to be related to amine-bisphosphonates, which include alendronate, pamidronate and risedronate. However, clodronate and etidronate, both non-amine-bisphosphonates, have also been implicated (1–3).

Health Canada received 27 domestic reports of suspected ocular and visual disorders associated with bisphosphonates since their introduction onto the Canadian market. Of these reports, 13 involved alendronate, 5 etidronate, 6 pamidronate and 3 risedronate. No cases of visual disorders have yet been reported in association with clodronate or zoledronic acid in Canada. Many factors, such as time marketed, exposure data and varying indications for the different products, can influence reporting rates of adverse effects in spontaneous reporting systems.

Indications of ocular inflammation may include eye pain, redness, abnormal vision (blurred or double vision, decreased vision, "floaters") and photophobia (1, 4). Although these ocular effects may be rare with bisphosphonates, health care professionals should be aware of their possibility.

The following guidelines have been suggested for the care of patients receiving bisphosphonates (1):

- Patients with visual loss or ocular pain should be referred to an ophthalmologist.
- Nonspecific conjunctivitis seldom requires treatment and usually decreases in intensity during subsequent exposure to a bisphosphonate.
- More than 1 ocular side effect can occur at the same time (e.g., episcleritis in conjunction with uveitis). In some instances, the drug may need to be discontinued in order for the ocular inflammation to resolve.

- For scleritis to resolve, even during full medical therapy, bisphosphonate therapy must be discontinued.

Extracted from the Canadian Adverse Reaction Newsletter, Volume 13(4), October 2003.

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Fluticasone and adrenal suppression

Inhaled corticosteroids are highly effective for the control of asthma and the prevention of exacerbations (1). However, there have recently been several reports worldwide of adrenal insufficiency in adults and children using inhaled corticosteroids (2–5). Although adrenal insufficiency can occur with any inhaled corticosteroid, it may be more common with fluticasone because of the drug's pharmacologic and pharmacokinetic properties, including its greater potency and hence lower equivalent dose (half the dose of either budesonide or beclomethasone) (2, 6, 7). In addition, this may result from higher-than-licensed doses of fluticasone being more widely prescribed in children than other inhaled corticosteroids (5).

The Health Canada database was searched for suspected adverse reactions involving endocrine disorders reported from 1996 to 2002, associated with fluticasone, budesonide and beclomethasone. There were no Canadian case reports of suspected adrenal insufficiency associated with the use of budesonide or beclomethasone.

There were 9 reports involving fluticasone, 5 of which involved children aged 4–13 years (where specified). Dosages (where specified) ranged from 250 to 1100 μg/d; in 4 cases the dose exceeded 1000 μg/d. Two patients experienced adrenal crisis; one was a boy (age unspecified), and the other was a 72-year-old man.

Adrenal insufficiency associated with inhaled corticosteroid use can occur because of systemic absorption of the corticosteroid and consequent suppression of endogenous glucocorticoids, which leaves insufficient adrenal reserve to respond to stressful stimuli (e.g., surgery, trauma and infection) (2, 3). Adrenal insufficiency may also result from abrupt discontinuation or non-compliance with treatment, which leads to acute steroid deficiency (2, 3). Signs and symptoms of adrenal suppression and crisis are nonspecific and include anorexia, abdominal pain, weight loss, fatigue, headache, nausea, vomiting, decreased level of consciousness, hypoglycaemia and seizures (3, 5).

Clinicians are reminded that, beyond a certain limit, increasing the dose of inhaled corticosteroids offers minimal benefit but increases the risk of systemic adverse effects (1, 7, 8). Once best results are achieved, the dose should be reduced at appropriate intervals to determine the minimum dose required to maintain control. In addition, different inhalation techniques and propellants can influence the portion of inhaled drug, and thus systemic bioavailability (6, 9).

Extracted from the Canadian Adverse Reaction Newsletter, Volume 13(4), October 2003.

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Adhesion prevention solutions in gynecological procedures

Intergel™ Adhesion Prevention Solution (0.5% ferric hyaluronate gel) has been indicated in Canada for use as an intraperitoneal instillate for the reduction of adhesions following peritoneal cavity surgery (1). It provides a transient, viscous, lubricant coating on peritoneal surfaces following surgical procedures. The product is contraindicated in patients with pelvic or abdominal infection.

Health Canada issued a class III medical device licence in1999. Since then, there have been post-market reports of suspected late-onset postoperative pain and repeat surgeries following onset of pain, noninfectious foreign-body reactions and tissue adherence associated with certain gynecological procedures. In some patients residual material was observed during surgery.

In March 2003, the product distributor issued an urgent worldwide voluntary withdrawal of Gynecare Intergel™ Adhesion Prevention Solution and advised that all use of the product be immediately discontinued (2, 3).

One report of a serious, unexpected reaction suspected to be associated with the product was received by Health Canada. A woman in her mid-30s (weight 64 kg) underwent laparoscopy and left fimbrioplasty in November 2002. Intergel™ Adhesion Prevention Solution was instilled at the end of the procedures. The following day the patient was admitted to hospital with peritonitis-like symptoms. She was given antibiotics empirically, and over 3 days her condition started to improve but she was still in pain. In January 2003 she presented with pelvic pain and was admitted to hospital for surgery. Residue of Intergel™ Adhesion Prevention Solution was washed out. Inflammation was observed, and many internal organs were adhered, with degradation of tissue.

Extracted from the Canadian Adverse Reaction Newsletter, Volume 13(4), October 2003.

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Treatment study for West Nile virus

A clinical trial evaluating an experimental treatment for patients infected with West Nile virus (WNV) has begun enrolling volunteers at 36 sites In the USA. This study is part of a larger effort by the National Institutes of Allergy and Infectious Diseases (NIAID) to develop new ways to prevent and treat the disease which appears to be spreading more quickly and more widely than during 2002.

The new study will assess whether WNV-infected individuals given antibodies to the virus are better able to fend off the severe symptoms of WNV, such as encephalitis, that contribute to the deaths of many individuals who become infected. Immunoglobulin treatment has been developed from the plasma of Israeli donors who have high levels of antibodies to WNV which is endemic in Israel. This study will provide information on safety and efficacy of this treatment in preventing death or neurologic disability and will help characterize the natural history of severe WNV infection.

The study seeks to enroll 100 hospitalized patients 18 years of age or older who have WNV-related encephalitis or are determined to be at risk of developing encephalitis based on clinical symptoms and the presence of antibodies to the virus. Patients will be assigned at random to one

of three groups. Each participant will receive a single-dose infusion of drug or placebo.

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Blue discoloration and death from FD&C Blue No. 1

The US Food and Drug Administration (FDA) has advised that several reports of toxicity, including death, have been associated with the use of FD&C Blue No. 1 (Blue 1) in enteral feeding solutions. In these reports, Blue 1 was intended to help in the detection and/or monitoring of pulmonary aspiration in patients being fed by an enteral feeding tube.

Reported episodes were manifested by blue discolouration of the skin, urine, faeces, or serum and some were associated with serious complications such as refractory hypotension, metabolic acidosis and death. Case reports indicate that seriously ill patients, particularly those with a likely increase in gut permeability (e.g., patients with sepsis), may be at greater risk for these complications. Because these events were reported voluntarily from a population of unknown size, it is not possible to establish the incidence of these episodes.

A causal relationship between systemic absorption of Blue 1 and the reported serious and life-threatening patient outcomes (including death) has not been definitively established. Indeed, it would be very difficult to establish a clear, causal relationship in the setting of complex medical issues often seen in patients receiving feedings via enteral tubes. However, in vitro evidence that Blue 1 can be a mitochondrial toxin lends plausibility to the idea that Blue 1 could cause these kinds of serious adverse effects if significant or persistent serum levels of the dye were to occur.

From the reports, it appears that neither the concentration nor the total amount of Blue 1 used in the enteral feeding solutions was unusually high compared to other patients in whom no toxicity was observed. Thus, if there is a causal relationship between the dye and the serious outcomes, there could be underlying patient-related factor(s) that allow significant absorption of Blue 1 in some enterally fed patients. A cause-and-effect relationship has not yet been clearly established.

FD&C Blue No. 1 is a water-soluble dye allowed by the FDA for use in foods, drugs and cosmetics, based on numerous studies in animals. The dye is batch certified by the FDA and is widely used in food products. There have been no reports of toxicity associated with general use. However, there has been no evaluation by the FDA of the sensitivity and specificity of its use in tinting of enteral feedings.

As of September, 2003, the FDA is aware of 20 cases from the scientific literature or in FDA post-marketing adverse event reports associating the use of blue dye in tube feedings with blue discoloration of body fluids and skin, as well as more serious complications. There have been 12 reported deaths and one case with an unknown outcome.

In more than 75% of all reported cases, patients had a reported history of sepsis (and therefore likely altered gut permeability) before or during systemic absorption of Blue 1.

Time of onset of toxicity from first use of Blue 1 varied from several hours to 20 days of continuous use in enteral feedings.

At this time, the FDA believes practitioners should be aware of the following points:

- Use of Blue 1-tinted enteral feedings for detecting aspiration has been associated with several serious adverse events, including death, although a direct causal relationship has not been definitely established.
- The safety of Blue 1-tinted enteral feedings for detecting aspiration has not been documented. Based on the reports received to date, patients at risk for increased intestinal permeability, which includes those with sepsis, burns, trauma, shock, surgical interventions, renal failure, celiac sprue, or inflammatory bowel disease, appear to be at increased risk of absorbing Blue 1 from tinted enteral feedings.
- In addition to the possibility of systemic toxicity, Blue 1-tinted enteral feedings may interfere with diagnostic stool examinations, such as the hemoccult test.

• Other blue dyes, such as methylene blue and FD&C Blue No. 2, may have similar if not greater toxicity potential than Blue 1 and would not be appropriate replacements.

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Atazanavir and tenofovir combination cautioned

The manufacturer of atazanavir has informed clinicians of new pharmacokinetic (PK) data concerning coadministration of atazanavir sulfate (Reyataz®) with tenofovir disoproxil fumarate (DF) (Viread®). Two studies have been conducted to evaluate potential PK interaction and an additional ongoing clinical study has provided preliminary data on the safety profile of this combination. Data from these trials are currently under review by the US Food and Drug Administration.

The following observations were made from three trials:

1. Study AI454–181: In healthy volunteers atazanavir AUC and C_{min} were decreased by approximately 25% and 40%, respectively, when unboosted atazanavir sulfate 400 mg was coadministered with tenofovir DF 300 mg once daily (QD) as compared to atazanavir sulfate alone. In addition, an increase of approximately 24% in tenofovir AUC was observed.

2. Study PUZZLE 2 (ANRS 107): Atazanavir AUC and Cmin were decreased by approximately 25% and 23%, respectively, when atazanavir sulfate 300 mg and ritonavir 100 mg (boosted atazanavir sulfate) were coadministered with tenofovir DF 300 mg QD, as compared to atazanavir sulfate 300 mg and ritonavir 100 mg administered without tenofovir DF to HIV-infected patients.

For the combination of boosted atazanavir sulfate with tenofovir DF, the atazanavir AUC and C_{min} observed in the Puzzle 2 study were approximately 1.2 and 4-fold higher than the respective values observed for unboosted atazanavir sulfate, 400 mg given alone, to healthy volunteers in Study AI424-181.

3. Study AI424-045: Interim safety data from an ongoing clinical trial suggest that the treatment emergent adverse events of moderate or severe intensity are comparable for boosted atazanavir sulfate in treatment-experienced patients and for unboosted atazanavir sulfate treated patients in other clinical trials.

Based on these results

• Clinicians should use caution when administering unboosted atazanavir sulfate with tenofovir DF. Unboosted atazanavir sulfate may be less effective due to decreased atazanavir concentrations in patients taking atazanavir sulfate and tenofovir DF. As a result, the coadministration of unboosted atazanavir sulfate with tenofovir DF may lead to loss or lack of virologic response and possible resistance to atazanavir sulfate

- If atazanavir sulfate is coadministered with tenofovir DF, consideration should be given to administering atazanavir sulfate 300 mg with ritonavir 100 mg and tenofovir DF 300 mg (all as a single daily dose with food), until additional data are obtained. Coadministration of atazanavir sulfate 300 mg and ritonavir 100 mg QD is currently under clinical investigation.

The increase in tenofovir AUC does not appear to be associated with increased toxicity over 24 weeks.

Reference: Communication from Bristol Myers Squibb on http://www.fda.gov/medwatch 8 August 2003.

Rofecoxib, celecoxib and cardiovascular risk

In a randomized controlled trial of the efficacy of rofecoxib in rheumatoid arthritis (the VIGOR study) the incidence of myocardial infarction was significantly greater with rofecoxib than with the comparator drug, naproxen (0.4% vs 0.1%) (1). While it was postulated that naproxen might have a cardioprotective effect, similar to that with aspirin, the result also raised the possibility that rofecoxib might be prothrombotic, leading to an elevated rate of myocardial infarction (2). Two factors in the VIGOR study which may have increased the risk of cardiovascular events were the high dose of rofecoxib used (50 mg daily; approved dose 12.5–25 mg daily) and the exclusion of the use of aspirin by participants in the study (2). Retrospective analysis indicated that aspirin for cardiovascular prophylaxis was indicated in 4% of the patients in the VIGOR study (1). Thirty-seven percent of the myocardial infarctions occurred in this 4% (3).

A recent large-scale cohort study has provided support for the view that the risk of cardiovascular events with rofecoxib may be dose-related (4). In the study, new users of high dose rofecoxib had a relative risk of serious coronary heart disease (CHD) of 1.93 compared with non-users of an non-steroidal anti-inflammatories (NSAIDs). The study found no increased risk of CHD among users of other NSAIDs, including celecoxib, or among users of lower doses of rofecoxib, and no protective effect with naproxen.

At present the evidence for an association between rofecoxib and a risk of cardiovascular events is inconclusive and indirect. The evidence for an effect with celecoxib is even weaker (2, 3).

Reflecting the current data, the Australian Adverse Reactions Advisory Committee (ADRAC) wishes to advise prescribers of the following:

- There may be an increased risk of cardiovascular and cerebrovascular disease with rofecoxib and celecoxib.
- The increase in risk seems to be higher in those with pre-existing cardiovascular disease.
- The risk appears to be greater with rofecoxib than with celecoxib, and appears to be dose-related.
- Rofecoxib should not be used at doses exceeding the maximum approved dose (25 mg/day).
- Cardiovascular risk should be evaluated before prescribing a coxib.

Some authors have advised taking low-dose aspirin with celecoxib or rofecoxib in patients with cardiovascular risk factors (3). However, aspirin, even in low dose, has the potential to reduce the gastroprotective benefit of the coxibs.

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 22, Number 5, October 2003.

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Convulsions and blood dyscrasias with mirtazapine

Mirtazapine (Remeron®, Avanza®, Mirtazon®), an antidepressant, antagonizes central alpha$_2$ adrenoceptors to cause an increase in noradrenaline and serotonin release. It is also a histamine

H_1 receptor antagonist, causing sedation, but has little anticholinergic activity. From May 2001 to May 2003, almost 500 000 funded prescriptions were dispensed.

The Australian Adverse Reactions Advisory Committee (ADRAC) has received 253 reports for mirtazapine. Common reactions reported are presented in the table below. A prescription event monitoring (PEM) study conducted in England of over 13 000 patients taking mirtazapine found that the most frequent adverse reactions were drowsiness/sedation and malaise/lassitude (5.8% and 2.8% of patients in the first month) (1).

Potentially serious reactions reported to ADRAC are convulsions (16 reports) and blood dyscrasias (15). None of the 16 patients who experienced convulsions with mirtazapine were known to have epilepsy. Mirtazapine was the only drug taken in eight of the cases. No cases of convulsions were identified in the PEM study.

Common reactions reported to ADRAC with mirtazapine 2001–2003

Reactions	Number of reports
oedema	33
anxiety/agitation	24
myalgia/arthralgia	24
sedation	23
skin reactions	20
blood dyscrasias	15
convulsions	16
hyperkinesis	15
dizziness	15
nightmares	14
increased weight	14
diarrhoea	11
nausea/vomiting	11
hepatic reactions	10
hallucination	9
serotonin syndrome	4

The blood dyscrasias reported were neutropenia (8), thrombocytopenia (6), lymphopenia (1) and pancytopenia (1). Two patients had fever with neutropenia. The time to onset was ≤ 2 months in 8 out of the 11 reports where this information was provided. Mirtazapine was the only suspected drug in nine of the blood dyscrasia reports.

Health professionals should be alert for signs of blood dyscrasias (fever, sore throat, petechiae etc.) in users of mirtazapine.

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 22, Number 5, October 2003.

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Safety and Efficacy issues
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Anti-epileptic drugs, pregnancy and fetal malformations

For some decades, an association has been recognized between maternal epilepsy and an increased risk of fetal malformation. Although inadequately controlled epilepsy is associated with dangers to mother and fetus, anti-epileptic drugs (AEDs) might cause adverse consequences in the fetus (1).

The Australian Adverse Reactions Advisory Committee (ADRAC) receives occasional reports of fetal malformations (FMs) associated with the use of AEDs in pregnancy. However, for many of these reported malformations, there are few published prospective data in human pregnancy indicating whether the AEDs involved increase risk. To address this lack, prospective pregnancy registers have been established in Australia, Europe, North America, and the United Kingdom.

Analysis of the 40-month data from the ongoing Australian Pregnancy Register for Women on Antiepileptic Medication has yielded important and clinically relevant information (2). Out of 403 pregnancy outcomes for women taking AEDs, 87.8% resulted in a healthy live birth, and 6.5% had an FM. (The remainder had spontaneous abortions or premature death in utero.) The FM rate was significantly greater in pregnancies exposed to valproate in the first trimester (16.0%) compared with those exposed to all other AEDs (2.4%). Furthermore, the mean daily dose of valproate was significantly higher in those with FMs than in those without FMs.

A recently published, prospective Finnish study of 970 pregnancy outcomes in women with epilepsy also found an association between the use of valproate in pregnancy and FM; control group: pregnancies in women with epilepsy not using AEDs in the first trimester) (3). Increased risks were also seen with carbamazepine and oxcarbazepine, and with low serum folate concentration in early pregnancy.

Prescribers should review the medication of women on AEDs in pre-pregnancy planning. Treatment should aim to maximize seizure control while minimizing the risk of FM. Folic acid supplementation prior to conception and during the first trimester is desirable in all pregnancies, especially in those women taking AEDs.

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 22, Number 5, October 2003.

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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.

Aspects of Quality Assurance

Supplying quality medicines for filariasis elimination

Lymphatic filariasis is a disfiguring, disabling disease transmitted by infected mosquitoes. It is caused by threadlike parasitic filarial worms which lodge in the lymphatic system and live for four to six years, producing millions of immature microfilaria that circulate in the blood. It is a serious public health and socioeconomic problem in many tropical and sub-tropical countries.

Lymphatic filariasis is ranked as the second largest cause of long-term disability (1). More than 40 million people are seriously incapacitated and disfigured by the infection and, in India alone, the economic impact due to lost work and decreased productivity is estimated at US$ 842 million annually (2).

Mass administration of DEC

In 1997, the World health Assembly resolved to eliminate lymphatic filariasis as a public health problem by the year 2020 through interruption of transmission and control of morbidity. The Global Programme to Eliminate Lymphatic Filariasis (http://www.who.int/ctd/filariasis) set out to achieve this through measures including community-wide mass drug administration (3).

To fulfil this mandate, it was estimated that 15 years' supply of diethylcarbamazine citrate (DEC) was needed — representing approximately 15 billion quality assessed tablets, manufactured according to good manufacturing practices (GMP) by reliable companies able to deliver on time (4, 5). Good manufacturing practices (GMP) ensures that products are consistently produced to the standards appropriate for their intended use and product specifications (6).

In order to identify sources of DEC, information was sought from:

- Regulatory authorities willing to supply information on manufacturers that had registered DEC for sale in countries where lymphatic filariasis is a public health problem.
- Lymphatic filariasis programmes which had purchased DEC.
- Lymphatic filariasis experts from around the world having information on manufacturers of DEC.
- Organizations such as the International Generic Pharmaceutical Alliance, British Generic Association, and the on-line network, E-Drug (7).

A search was also launched through the Internet, advertisements in international journals, and pharmaceutical guides/compendia.

In November 1999, an inventory of DEC manufacturers was prepared. The inventory included only manufacturers that supplied information on quality assurance in their manufacturing sites. Because of the geographical distribution of the disease, many commercial manufacturers of DEC tablets were identified in the developing world, with approximately half of these in India.

Developing a modern assay for DEC

In March 2000, the Programme organized an informal consultation to secure consensus on appropriate standards and guidelines proposed for DEC active pharmaceutical ingredient (API) and tablets and to discuss currently available assay methods. Participants recommended that WHO develop a modern stability-indicating assay for DEC that meets current standards, including dissolution. An HPLC analytical method was developed in Switzerland and validated by independent laboratories in Germany, India and Sri Lanka. The United States Pharmacopeia and the Indian Pharmacopoeia have adopted the new modern stability-indicating method for DEC (8, 9).

DEC prequalification process

Only manufacturers are eligible for prequalification within the DEC Project. Before an on-site inspection can take place, the Project team requires that an independent laboratory evaluate DEC and the manufacturer is requested to complete the *WHO Information Questionnaire for Prospective Suppliers of Pharmaceutical Prod-*

ucts. This provides information on manufacturing facilities (the plant master file), all technical operations, the DEC master file, the quality assurance system used by the company, validation of analytical methods, and quality control laboratory, GMP and Good Laboratory Practices (GLP) used by the company and at the DEC manufacturing site. Manufacturers on the Inventory are asked if the company will permit an inspection team to conduct an in-depth inspection of the manufacturing site for DEC.

DEC manufacturers were inspected by a skilled team established to verify on-site compliance with GMP. Inspectors were chosen for their experience in production of pharmaceuticals, APIs and bulk chemicals, quality assurance, inspection, and working experience in a signatory country of the Pharmaceutical Inspection Collaboration Scheme (PIC/S).

The inspection team included WHO staff and former senior members of:

- a European regulatory agency, signatory of the PIC/S;
- a multinational pharmaceutical company;
- a pharmaceutical manufacturing facility in Australia.

The manufacturer is requested to provide information on stability studies, a copy of the most recent batch record for manufacturing and packaging, information on sources of reference substances, active pharmaceutical ingredients, and all other materials used in manufacture. Additionally, the company must test the stability of DEC according to the WHO Stability guidelines for Zone IV (hot and humid conditions) (10) and ICH guidelines for evaluation of stability of pharmaceuticals in Zone IV (Quality Topic Q1F) (11)[1].

The team requests national/state regulatory authorities to nominate inspectors to accompany the inspection team. It discusses the DEC Project with the regulatory authorities, inspectors, and the Minister of Health for the state or country. The inspection team uses WHO guidelines during the inspection as a general guide to GMP (6).

Prequalification[2] of DEC manufacturers

A manufacturer having an acceptable compliance profile is confirmed as a prequalified DEC provider (see Table 1). Prequalification is valid for 2 years after which time manufacturers should be re-inspected and re-qualified, preferably by or with assistance of the national drug regulatory authority, through an evaluation of recent documentation and on-site inspection.

Table 1. Prequalification process for DEC Manufacturers

Phases of prequalification	No. of manufacturers	Responses
1. Initial call for proposals	–	Regulatory and government authorities, known manufacturers, filariasis programmes
2. Suppliers/manufacturers providing basic information regarding GMP and G(QC)LP at manufacturing site	43	Australia, Bangladesh, Belgium, Brazil, Denmark, Egypt, France, India, Indonesia, Ireland, Malaysia, Malta, Netherlands, Sri Lanka, Switzerland, Thailand, United States of America
3. Manufacturers audited on-site	13	Belgium, India, Malaysia, Singapore, Sri Lanka
4. Manufacturers prequalified	5	Belgium, India, Sri Lanka
5. Manufacturers currently listed	3	India

[1] WHO and ICH have recently harmonized the approach to stability testing for Zone IV, see WHO Expert Committee on Specifications for Pharmaceutical Preparations. Technical Report Series, No. 908. p. 13 (2003).

[2] See boxed text on page 247.

Although a number of manufacturers have been identified by the DEC project, not all were compliant on various criteria and tests so that, as of November 2002, the prequalified DEC tablet manufacturers are:

- Panacea Biotech, New Delhi, India; and
- Unichem Laboratories, Goa, India.

There is one prequalified DEC API manufacturer:

- Syntholab Chemicals and Research, Mumbai, India.

WHO purchases DEC tablets from prequalified manufacturers only. Country programmes are also strongly encouraged to use prequalified DEC manufacturers for their purchases.

Developing a quality surveillance system

The Programme is currently developing an ongoing system to monitor the quality of purchased DEC. Randomized collection of samples from each of the manufacturers is handled by an independent company before laboratory testing is carried out to determine whether DEC meets internationally recognized standards. WHO encourages adoption of this ongoing quality surveillance system in national programmes.

Savings linked to bulk purchase

Procurement officials know that increasing the number of tablets purchased normally reduces the price per unit. Experience in WHO has also shown that consolidating orders for many countries based on the projections of an annual global forecast reduces the price even further. Within the project, orders were consolidated for several countries and — utilizing funds provided to WHO by donors (12) — the price obtained per 1000 DEC tablets was 30 % to 45 % lower when compared to that paid in 1999. This process demonstrates that a centralized process for purchasing a large number of tablets for several countries lowers the cost. The initiative saves money which enables purchase of additional amounts of DEC tablets while at the same time assuring the highest standards of quality. (See Table 2 below).

Capacity building

The Programme has built capacity in countries affected by lymphatic filariasis through provision of training and expertise while improving compliance with GMP and GLP.

Through on-site inspections, both the manufacturer and national regulatory personnel have the opportunity to gain experience, learn, and improve production procedures and quality assurance systems. During an inspection, the team explains why a procedure is not acceptable or acknowledges compliance. During the inspection, the team encourages participants to use the exercise as a learning experience, thereby contributing to expanding understanding and improving application of internationally recognized standards.

The DEC Project collaborates with manufacturers to ensure that they implement corrective action and maintain GMP and GLP during the entire period of validity of the prequalification status for DEC. The initiative to eliminate lymphatic filariasis benefits from all improvements that manufacturers make. The manufacturer is provided with a report listing the observations made during the inspection and a summary of any deficiencies in GMP or GLP.

Since initiation of the project in August 1997, WHO has invested both technical and human resources to:

- develop and validate new analytical methods for DEC (13, 14);
- perform dissolution tests of DEC tablets;
- test DEC API and DEC tablets in an independent laboratory;

Table 2. Purchase of DEC tablets by WHO*

Strength	2000	2001	2002	2003	Total tablets
50 mg	22.2	111.02	17.13	5.43	155.78 million
100 mg	—	37.96	40.82	107.6	186.38 million

** Annual Report on Lymphatic Filariasis, 2001 WHO/CDS/CPE/CEE/2002.28, and Annual Report on Lymphatic Filariasis 2002. WHO/CDS/CPE/CEE/2003.38*

- conduct various on-site inspections; and
- provide necessary technical assistance and follow-up.

The benefits gained from the programme are therefore substantial. The initial investment is designed to give long term benefit by ensuring that national programmes to eliminate lymphatic filariasis administer quality DEC tablets in 60 of the 80 endemic countries during the 15 years of mass drug administration.

Conclusion

The prequalification process has ensured that DEC tablets and active pharmaceutical ingredients have been manufactured in compliance with international standards. In this way, supplies of DEC have been made available for the requirements of the Programme on Elimination of Lymphatic Filariasis at a low cost.

The prequalification process has functioned very successfully. The project must now ensure that manufacturing is sustained and sufficient quantities of quality DEC are provided to meet the long-term requirements of the Programme. In order to meet the global forecast, bulk purchasing through an international competitive bid mechanism must continue to be strengthened to enable cost reduction leading to tangible savings. (15).

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Unified standards for prequalification

The "prequalification" of diethylcarbamazine (DEC) described in this article commenced before the unified general prequalification procedures were adopted by the World Health Organization. The procedure for assessing the acceptability, in principle, of pharmaceutical products for purchase by United Nations agencies is published as Annex 8 in: *World Health Organization, Report of the Expert Committee on Specifications for Pharmaceutical Preparations, Technical Report Series No. 908, pp. 113–124 (2003).* More information about the joint prequalification project of the UN agencies, WHO, UNICEF, UNAIDS and UNFPA, with the support of the World Bank, is available from the website: http://www.who.int/medicines. The "prequalification" of diethylcarbamazine (DEC) does not necessarily follow all the principles and standards of the unified prequalfiication project described above.

Regulatory and Safety Action

Recommended influenza vaccine for 2004 (Southern hemisphere)

World Health Organization — National Authorities are responsible for recommendations regarding the use of influenza vaccine and should approve the specific vaccine viruses used in each country.

It is recommended that influenza virus vaccines to be used in the 2004 season (Southern hemisphere winter) contain the following:

- an A/New Caledonia/20/99 (H1N1)-like virus;
- an A/Fujian/411/2002 (H3N2)-like virus {A/ Kumamoto/102/2002 and A/Wyoming/3/2003 an egg-grown A/Fujian/411/2002 (H3N2)-like virus}
- a B/Hong Kong/330/2001-like virus {Currently used vaccine viruses include B/Shandong/7/97, B/Hong Kong/330/200, B/Hong Kong/1434/ 2002. B/Brisbane/32/2002 is also available as a vaccine virus.}

Information concerning reagents for use in laboratory standardization of inactivated vaccine and reference strains for antigenic analysis is available on http://www.who.int/influenza.

Reference: *Weekly Epidemiological Record*, No. 43. 24 October 2003.

Daclizumab: safety alert

North America — Two new warning statements have been added to the prescribing information for daclizumab (Zenapax®) indicated for for the prevention of graft rejection. These include increased mortality in a cardiac transplant study and updated information regarding hypersensitivity reactions.

The use of daclizumab as part of an immunosuppressive regimen including cyclosporine, mycophenolate mofetil, and corticosteroids may be associated with an increase in mortality. In a randomized, double-blind, placebo-controlled trial of daclizumab for the prevention of allograft rejection in 434 cardiac transplant recipients receiving concomitant cyclosporine, mycophenolate mofetil and corticosteroids, mortality at 6 and 12 months was increased in those patients receiving daclizumab compared to those receiving placebo, sometimes through a higher incidence of severe infections. Concomitant use of antilymphocyte antibody therapy may also be a factor.

Severe, acute (onset within 24 hours) hypersensitivity reactions including anaphylaxis have been observed both on initial exposure to daclizumab and following re-exposure. These include hypotension, bronchospasms, wheezing, laryngeal oedema, pulmonary oedema, cyanosis, hypoxia, respiratory arrest, cardiac arrhythmia, cardiac arrest, peripheral oedema, loss of consciousness, fever, rash, urticaria, diaphoresis, pruritus, and/or injection site reactions. If a severe hypersensitivity reaction occurs, therapy with daclizumab should be permanently discontinued. Medications for the treatment of severe hypersensitivity reactions including anaphylaxis should be available for immediate use. Patients previously administered daclizumab should only be re-exposed to a subsequent course of therapy with caution. The potential risks of such re-administration, specifically those associated with immunosuppression, are not known.

Additionally, the following adverse reactions occurred more frequently in paediatric transplant patients than adult transplant patients: diarrhoea, postoperative pain, fever, vomiting, aggravated hypertension, pruritus and infections of the upper respiratory and urinary tracts.

Reference: Communication from Roche Pharmaceuticals available on http:// www.fda.gov/medwatch and www.hc-sc.gc.ca dated 6 November 2003.

Nefazodone discontinued

Canada — In consultation with Health Canada, the manufacturer of nefazodone (Serzone-5HT$_2$®) has decided to discontinue sales of the product from the market in Canada effective 27 November

2003. Nefazodone has been associated with adverse hepatic events including liver failure requiring transplantation.

Nefazodone is indicated for the symptomatic relief of depressive illness. Since introduction in 1994, nefazodone has been temporally associated with hepatic adverse events such as jaundice, hepatitis and hepatocellular necrosis in patients receiving therapeutic doses. As of December 2002, there were 51 Canadian reports of hepatotoxicity, ranging from no symptoms to transplantation, suspected to be associated with nefazodone use. One of two transplant recipients subsequently died. Cases of liver injury have occurred as early as a few weeks after initiation of therapy or after continuous use for up to 3 years. To date, no risk factor to predict patients who will develop irreversible liver failure with nefazodone has been identified. Also, no clinical strategy, such as routine liver function tests, could be identified to reduce the risk of liver failure.

Reference: Communication from Bristol Myers Squibb, 2 October 2003 on www.hc-sc.gc.ca

Levomethadyl discontinued

United States of America — The sale and distribution of levomethadyl hydrochloride acetate (Orlaam®) oral solution, 10 mg/mL will be discontinued after the current inventory is depleted in the first quarter of 2004. Since the introduction of levomethadyl in 1995, the manufacturer has received increasing reports of severe cardiac-related adverse events, including QT interval prolongation (15), Torsades de Pointes (8) and cardiac arrest (6). Other cardiac-related adverse events have also been reported, including arrhythmias, syncope, and angina. These events led to the removal of levomethadyl from the European market in March 2001. A very small number of patients may benefit from levomethadyl, but the risk of continued distribution and use no longer outweighs the overall benefits.

Levomethadyl is a synthetic opioid agonist solution indicated for the management of opiate dependence, reserved for the treatment of opiate-addicted patients who fail to show acceptable response to other adequate treatments for opiate addiction.

Due to the forecasted unavailability shortly after the beginning of 2004, no new patients should be initiated on levomethadyl therapy. For existing patients, it is extremely important for healthcare providers to transfer patients to alternative treatments as soon as possible prior to the product's unavailability. Patients maintained on levomethadyl may be transferred directly to methadone. Because of the difference between the two compounds' metabolites and their pharmacological half-lives, it is recommended that methadone be started on a daily dose at 80% of the levomethadyl dose being replaced; the initial methadone dose must be given no sooner than 48 hours after the last levomethadyl dose. Subsequent increases or decreases of 5 to 10 mg in the daily methadone dose may be given to control symptoms of withdrawal or, less likely, symptoms of excessive sedation, in accordance with clinical observations.

Reference: Communication from Roxane Laboratories on http:// www.fda.gov/medwatch

Daptomycin: new class of antibiotic approved

United States of America —The Food and Drug Administration (FDA) has announced the approval of daptomycin (Cubicin®) injection for the treatment of complicated skin and skin structure infections, including major abscesses, post-surgical skin wound infections, and infected ulcers. Daptomycin is the first of a new class of antibiotics called cyclic lipopeptide antibacterial agents.

Daptomycin is specifically indicated for the treatment of complicated skin and skin structure infections caused by susceptible strains of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant strains), *Streptococcus pyogenes*, *S. agalactiae*, *S. dysgalactiae* subspecies *equisimilis* and *Enterococcus faecalis* (vancomycin-susceptible strains only). Daptomycin is not indicated for the treatment of pneumonia.

Approval was based on a review of clinical studies involving over 1400 adults. Adverse events reported in the clinical studies were mild to moderate in intensity and included: gastrointestinal disorders, injection site reactions, fever, headache, insomnia, dizziness, and rash.

Blood tests showing muscle injury were found rarely in patients in clinical trials. Most of these patients had no symptoms, and the blood tests returned to normal after therapy. Patients receiv-

ing daptomycin should be monitored for the development of muscle pain or weakness. Creatine phosphokinase (CPK) levels should be monitored weekly. Those who develop unexplained elevations in CPK should be monitored more frequently.

Reference: *FDA Talk paper*, T03-66. 12 September 2003 on http:// www.fda.gov

Tetrahydrogestrinone: grave risks to health

United States of America —Tetrahydrogestrinone (THG) is reportedly used by athletes to improve their performance. The Food and Drug Administration (FDA) has determined that THG is an unapproved new drug and is working with other Federal law enforcement agencies to aggressively engage, enforce, and prosecute those firms or individuals who manufacture, distribute, or market THG. FDA believes that its use may pose considerable risks to health.

THG may be represented as a dietary supplement but it is a purely synthetic "designer" steroid derived by simple chemical modification from another anabolic steroid that is explicitly banned by the US Anti-Doping Agency.

This substance is closely and structurally related to two other synthetic anabolic steroids, gestrinone and trenbolone.

Reference: *FDA statement*. 28 October 2003.

Coronary Stents and thrombosis

United States of America —The Food and Drug Administration (FDA) has informed physicians that more than 290 reports of thrombosis (clotting) have occurred one to 30 days after the procedure to implant a Cordis Corporation's Cypher Coronary Stent®.

In more than 60 of these reports, use of the device was associated with the death of the patient; in the remainder, the device was associated with injury requiring medical or surgical intervention. FDA has also received more than 50 reports, including some deaths, that are considered to be possible hypersensitivity reactions. The symptoms include: pain, rash, respiratory alterations, hives, itching, fever, and blood pressure changes.

However, hundreds of thousands of patients have been successfully treated with the Cypher® stent. FDA does not have enough information to determine whether the incidents of thrombosis and hypersensitivity reactions differ from those experienced with bare metal stents.

The Cypher® stent was approved in April 2003 for patients undergoing angioplasty procedures to open clogged coronary arteries. The stent, a cylindrical metal mesh, is designed to keep the arteries from re-clogging after the procedure. It is coated with a thin polymer containing the drug sirolimus that is slowly released and is intended to reduce the rate of re-blockage that occurs with other stents.

The FDA is requiring the manufacture to conduct a 2000-patient post-approval study and continue evaluating patients from ongoing clinical trials to assess the long-term safety and effectiveness of the stent and to look for rare adverse events that may result from use of the product.

Reference: *FDA Talk Paper*, T03-71. 29 October 2003.

Bicalutamide: do not use in localized prostate cancer

Canada — In November 2002, bicalutamide (Casodex®) 150 mg, was conditionally approved in Canada for patients with localized prostate cancer inappropriate for surgery or radiation therapy. Approval was based on the promising nature of clinical evidence and time to objective progression.

The manufacturer has now alerted healthcare professionals to important emerging safety information arising from a planned second analysis of the Early Prostate Cancer (EPC) trial programme which compared bicalutamide with placebo.

For the progression-free survival endpoint, there continues to be a significant reduction in the risk of experiencing disease progression after 5.4 years of follow-up. However, conclusions can only be made regarding early benefits or risks. Patients treated in the adjuvant setting show no differences in survival, though survival data in this setting are still relatively immature at this time.

In view of these data, and in the absence of factors to suggest high risk of disease progression, it is recommended that clinicians discon-

tinue bicalutamide in patients with localized prostate cancer otherwise undergoing watchful waiting. It should be noted that metastatic prostate cancer patients taking bicalutamide 50 mg per day are not affected by the new information (1).

United kingdom — The Committee on Safety of medicines has advised that for patients with localized prostate cancer, the balanced risk benefit of biculatimide is unfavourable and the product is no longer licensed for the treatment of this condition. Other approved uses are not affected.

Patients receiving biculatimide for localized prostate cancer should be reviewed at the earliest opportunity and treatment discontinued (2).

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2. Communication from the Committee on Safety of medicines. 28 October 2003. info@mhra.gsi.gov.uk

Recombinant antihaemophilic factor: dose monitoring required

Canada — Recombinant antihaemophilic factor [BDDrFVIII] (ReFacto®) has been licensed in Canada since 2002, and is indicated for the control and prevention of haemorrhagic episodes and for routine and surgical prophylaxis in patients with haemophilia A (congenital factor VIII deficiency or classic haemophilia). ReFacto® does not contain von Willebrand factor and hence is not indicated in von Willebrand disease.

Reports of lack of effect, mainly in prophylaxis patients, have been received during clinical trials and post-marketing. Lack of effect and/or low factor VIII recovery has now been reported in other patients such as bleeding into target joints, bleeding into new joints, other bleeding or a subjective feeling by the patient of new onset bleeding.

In order to ensure an adequate therapeutic response, it is important to individually titrate and monitor each patient's dose, particularly when initiating treatment.

Reference: Communication from Wyeth, 15 September 2003 on http://www.hc-sc.gc.ca

Nimesulide-containing products reevaluated

European Union — Nimesulide, is a COX-2 inhibitor first launched in Italy in 1985. Since then, it has been marketed in about 50 countries throughout the world. Reports of adverse drug reactions, including hepatic reactions and a report of necrotizing fascitis leading to death, have led to a re-evaluation.

In July 2003, the Committee on Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal products (EMEA) determined that the benefit-risk profile of nimesulide-containing products for systemic and topical use is favourable. It recommended that use should be restricted to treatment of acute pain, symptomatic treatment of painful osteoarthritis and primary dysmenorrhoea for systemic formulations and symptomatic relief of pain associated with sprains and acute traumatic tendinitis for the topical formulation.

Reference: EMEA/CPMP/3754/03. 1 August 2003. http://emea.eu.org

Memantine approved for Alzheimer disease

United States of America — The Food and Drug Administration (FDA) has approved memantine (Namenda®), for the treatment of moderate to severe Alzheimer disease.

Alzheimer disease is a degenerative condition affecting memory, judgment and the ability to reason. The new drug — an N-methyl-D-asparate (NMDA) antagonist — is thought to work by blocking the action of the chemical glutamate. Although memantine helps treat the symptoms of Alzheimer disease in some patients, there is no evidence that it modifies the underlying pathology of the disease.

The first two double-blind studies, each of about six months duration, were conducted in the United States. The larger study of 400 patients was carried out in subjects already taking donepezil, a drug already approved for the treatment of Alzheimer disease. Both studies showed that patients on memantine experienced less deterioration in their symptoms compared to patients treated with placebo during the study. The third

study, conducted in nursing homes in Latvia, was a 12-week double-blind study in 166 patients with severe Alzheimer disease and also showed a statistically significant advantage of memantine over placebo.

Reference: *FDA News*, P03-82. 17 October 2003.

Virologic non-response in more HIV combinations

Spain — Lamivudine (Epivir®) and didanosine (Videx®) in combination with tenofovir (Viread™), should not be used as a triple antiretroviral therapy when considering a new treatment regimen for naïve or pre-treated HIV-1 infected patients.

A recent 24 week/24 patient study carried out to determine efficacy and safety has observed a high (91%) lack of virologic response in HIV patients treated with this combination. The precise nature of non-response in this study is not known.

The Committee on Proprietary Medicinal products (CPMP) of the European Medicines Evaluation Agency (EMEA) has requested more detailed information on the study. In the meantime the following action is recommended:

- No new patients should be initiated on a tenofovir + didanosine + lamivudine combination regimen.
- The viral load of patients currently administered this combination should be closely monitored. In the event of an increase, therapy should be adjusted accordingly.

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Personal Perspectives

Placebo or active control? Either, as long as it is in the patient's interest*

The appropriate use of placebo in controlled clinical trials is still debated. This article briefly reviews different conditions of applicability of the placebo dilemma in the light of patients' interests and needs. We also test our assumptions that (a) what should justify the authorization of new drugs is their proven superiority over the best available comparators; (b) superiority to placebo is only clinically meaningful in patients who cannot benefit from the standard active comparator; (c) non-inferiority of new drugs compared to available treatments can only be assessed when additional benefits over active controls are foreseeable and adequately tested. Ethical committees should advocate these principles in defence of patients' interests. Public funds should support independent clinical research, which would help address questions of high priority for public health, but be of no commercial appeal for industry

The discussion raised by the latest version of the Declaration of Helsinki (1) about the legitimacy of using placebo in controlled clinical trials is still alive. Temple and Ellenberg (2) state that the acceptability of placebo depends on whether the patient will be harmed by deferral of effective treatment. Emanuel and Miller (3) advocate a middle-ground alternative, which allows the use of placebo when no therapy is available for a given indication or when the lack of benefit (not necessarily harm) or the discomfort to patients receiving placebo is negligible. Lewis et al (4) argue that placebo-controlled trials remain the only means of assessing the efficacy of new medicines, whose potential advantages over recognised alternatives lie in areas other than efficacy.

The debate focuses on patients' well-being as the only aim of clinical investigation. Life, however, is different and the placebo or active-control dilemma can hardly be resolved in an environment essentially driven by the strong economic interests of the pharmaceutical industry where patients' needs and interests are not the only sources of clinical research hypotheses. In our opinion what matters is not so much the methodology as the aim and independent conduct of trials. Once identified, any clinical question that is truly relevant for patients and independently pursued would in itself imply the best way to be addressed. When the questions identified have only relative importance for patients, any methodological discussion on how best to answer them is an exercise of limited value.

Use of placebo not targeted to patients' needs

In order to maintain its level of profitability, the drug industry has to contain its risks and costs, and increase its revenues and market. One way to limit risks and costs is to use placebo trials, whenever possible, in order to obtain a slice of an existing market rather than to risk an expensive failure trying to prove an advantage over active comparators. Most placebo-control trials are done not because there are no alternatives, but because it is easier to show an effect and therefore to claim efficacy to the regulatory authorities.

The strategy is to position a new product so that its superiority can be suggested with advertising and incentives to doctors and pharmacists without having to prove it scientifically. A drug that is scientifically proven to be superior to its comparator is unlikely to need such efforts to sustain its sales and convince doctors to prescribe it. But efforts are certainly needed with most copies, which are by definition very similar: for most ACE-inhibitors, sartans, antidepressive agents or nonsteroidal anti-inflammatory drugs it is very difficult to make a choice on the basis of patients' needs (5), as these products were not developed to provide a better treatment in the first place.

Clearly, me-too drugs aim at finding a place in the market rather than in therapy. Therefore, the whole issue of clinical trials requires discussion of

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a fundamental question that is preliminary to any others about study design and controls: "Is it ethical to submit patients to clinical trials whose sole purpose is clearly to gain access to the market?"

Placebo is sometimes not used when it should be

Placebo-controlled studies in depressive or hypertensive patients resistant or intolerant to available therapies would be appropriate, as they would respond to a real need; patients resistant to current therapy would lose out from the lack of these studies. But in the eyes of drug companies this approach would mean gaining approval for a restricted indication and, consequently, a limited market and profits. This is why such trials are not usually done. That the use of placebo in these circumstances is not a satisfactory solution for pharmaceutical companies is demonstrated by the fact that often they do not avoid comparison with active controls, but only test the equivalence or — more often nowadays — the non-inferiority of new drugs with respect to the available comparators. Non-inferiority studies raise two major questions: one methodological, one substantial.

Placebo does not add to non-inferiority tests

The arguments raised (2–4) on the methodological deficiencies and inconsistent messages of non-inferiority trials are fully endorsed (6–8). What we object to here is that inclusion of a placebo arm would overcome the potential lack of sensitivity of this kind of study (2, 4). As was the case with trials for depression (9), the inclusion of placebo may show whether the test and control treatments are truly effective. However, even so, the claimed similarity of the test drug and the active comparator would remain an artefact: because of the weak power of the study in view of the small number of patients, this similarity may in fact hide important clinical differences (7–10).

According to pre-specified definitions, non-inferiority limits include an excess of outcome events associated with the test treatment. Two, five, or ten more deaths, strokes, fractures, interventions every hundred treated patients may not be considered enough to mark a difference between the new and the control drug, thus permitting the conclusion of non-inferiority of the former. A poorer outcome with the new drug than with current available treatment is not acceptable, even if better than in a concurrent placebo arm. Poor sensitivity is intrinsic to non-inferiority trials, which deliberately aim at overlooking differences rather than highlighting them.

As with superiority over placebo, non-inferiority to active comparators might also allow onto the market drugs that in fact are less active (or safe, tolerable, convenient, etc.) than those already available, usually with consolidated properties and a lower cost. Moreover, these approaches do not meet patients' or physicians' needs to define the place in therapy and respective roles of new and available treatments.

Active controls are not used as they should be

The solution of a methodological problem (sensitivity of non-inferiority trials) does not in any event dignify a hypothesis (non-inferiority of the test drug) that has no or little importance for patients. Besides sensitivity, the main problem with these trials is that they lack ethics (8). Here the point is not even about placebo or active control. Simply, these studies deliberately disregard patients' interests in favour of commercial ones. Non-inferiority studies do not provide any possible advantage to patients. Like placebo-controlled studies, they aim at claiming efficacy, and possibly additional advantages, without providing proof.

These trials only have an economic interest and we believe few patients would agree to participate if the industrial sponsor's message were clearly conveyed in the "informed consent" as follows: "I want to recruit a number of patients and let chance decide whether they should go on taking the effective treatment they are currently given, or try my new drug, which is not expected to be any better. To me it is enough to establish that my drug is equivalent to or not worse than the other one". It is surprising that these trials obtain clearance by Ethical Committees in the absence of other advantages.

The excuse for carrying out these trials is usually that physicians need several alternatives because not all patients respond the same way. But again, if this is the case, why not use placebo-controlled trials in patients not adequately responding to other treatments? In contrast, just as it does not solve methodological problems, the inclusion of a placebo arm in non-inferiority trials is even less likely to solve these ethical problems.

(Views expressed in signed contributions remain the responsibility of the authors.)

Placebo does not help distinguish true and false innovation

There may still be a place for non-inferiority trials when there are potential advantages for patients and/or the community, besides similar efficacy. A non-inferiority study can be regarded as ethical when a drug similar to its comparator in terms of efficacy may nevertheless have better safety, convenience, or cost-effectiveness: for example, a Cox-2 selective inhibitor with fewer gastrointestinal adverse effects, a sartan inducing less cough than ACE-inhibitors, an orally available iron chelator for children with thalassaemia, an estrogen patch replacing daily pills, a vaccine combination. What is important is that the claimed advantages and their impact on patients and/or the community be appropriately tested and documented, as is required for efficacy. This approach in fact implies documentation of superiority.

It is hard to envisage here any role for placebo (4): potential advantages should be assessed in comparison with any recognised active control, of course. The advantage should be pre-specified and serve as a guide for establishing an acceptable limit of non-inferiority, meaning the difference in outcome allowed for two products still to be considered similar. The excess of events allowed to document similar clinical efficacy while looking for other potential advantages should be explicitly justified: how many more deaths, infarctions, interventions, etc would we consider acceptable in testing (and possibly proving) that the new drug is actually, safer, better tolerated, easier to use, or cheaper than its comparator?

More independent clinical research as a solution

Most divergences on the use of placebo or active control would be minimised if public health interest were constantly kept as the primary objective. If the study plan and conduct reflect this, investigators' intellectual independence with respect to the tested hypothesis would be assured too. Financial interests can equally be covered when proven advantages are provided to individual patients or their community. In this respect, medicinal products cannot be regarded like any other product, because their value should only lie in the public health gains they provide, which need to be documented objectively.

Ethical Committees are urged to look more carefully at trial protocols to establish not only that no harm will result to patients involved in the trial but also whether the trials are appropriately designed to demonstrate any foreseeable benefit for patients for whom the drug is intended after its approval.

Public funds supporting independent clinical research play a critical role in helping the scientific community keep its intellectual freedom with respect to priority objectives, identification of clinical hypotheses and appropriate trial design. It also enables public health institutions to address questions that are not in the direct interests of industry (11), which cannot be expected to pursue, and fund, scientific and public health objectives that are not in line with — and may even be against — its commercial aims. In the United States health policy makers have correctly understood these principles and ensured an adequate level of funding for independent research.

Good examples are the results achieved with public funds for HIV/AIDS treatments at the time the public health interest for this area was particularly important (12). The same cannot be said at present for the European Community, which still has to develop its own policy in this area and decide on the level of funding it considers useful to cover the public health interest. It is important to note that independent research would also indicate to industry what kind of products public health needs, and could therefore be a powerful stimulus to re-orientate industrial clinical research too.

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Current Topics

WHO review of NICE in the United Kingdom

The National Institute of Clinical Excellence (NICE) is responsible for providing guidance to the National Health Service in England and Wales on the clinical- and cost-effectiveness of medicines and medical technologies. In 2002, NICE commissioned a series of internal reviews of their work, while an external review was carried out by the WHO Regional Office for Europe.

The WHO team of experts reviewed a series of technology appraisals and carried out extensive discussions with NICE staff, members of the Appraisal Committee and Technical Assessment Groups and other stakeholders during the course of two visits to NICE in 2003.

NICE was established as a Special Health Authority to address the introduction and use of new technologies and medicines within the United Kingdom National Health Service (http://www.nhs.uk.). The Review Team recognized that — in only four years — NICE had developed a well-deserved reputation for innovation and methodological development that represents an important model for technology appraisals internationally.

Achievements that are particularly valuable include:

• transparency surrounding the process of technology assessment.

• participation of different stakeholders and the inclusiveness of the approaches taken.

• commitment to using the best available evidence for decision-making.

• commitment of the technical and management staff.

• dedication of the appraisal team and Committee members.

The Review Team made the following recommendations which were drawn up with the aim to enhance operations within NICE and assist organizations with similar responsibilities in other countries. The full rassessment eport is avalable on: http://www.nhs.ukand http://www.nice.org.uk

Recommendations

The principles

• NICE should continue to develop operational procedures that are consistent with its core principles of transparency, consultation and inclusiveness with respect to stakeholders' involvement in evidence- gathering and decision-making. The NICE model of partnership in the scientific endeavour of health technology appraisal offers valuable international leadership.

• NICE should seek to reconcile the inherent contradiction between its principles of transparency and its acceptance of evidence for the decision-making process that a stakeholder deems to be confidential. NICE should continue the work already started on this issue to ensure that all material submitted for consideration can be made available to the public.

• The principle of transparency requires that NICE codifies and justifies the specific criteria used in decision-making. Difficult but important elements of this task are articulation of the ethical

and social value judgements, and definition of the interaction of these judgements with the appraisal of the scientific evidence used by the Appraisal Committee in reaching its decisions.

The process – general issues

• For drug and device technologies where a sponsor exists, the current hybrid process of HTA used by NICE may give rise to unnecessary duplication of effort. NICE may wish to consider using different approaches depending on the subject of the appraisal. The Review Team suggests that an effort be made to ensure that the Appraisal Committee is presented with a single set of analyses produced by the Technical Assessment Group that incorporates consultation with and input from the manufacturer(s).

Start of the process and topic selection

• The consultees' meeting should become a formal 'Preliminary Exchange of Evidence', at which time all stakeholders should be asked to provide details of what they propose to submit. Only in extraordinary circumstances should the Technical Assessment Group accept to include, as part of the review, information over and above that declared for submission by the stakeholders at this meeting.

• More attention needs to be paid to the important task of setting the Scope of the appraisal. The general goal is to give timely and comprehensive guidance to the Technical Assessment Groups on the question(s) to be addressed by the Appraisal Committee, thereby reducing the risk of mismatch between the technical assessment report and the needs of the Appraisal Committee.

• Stakeholder submissions should be required to be lodged as soon as possible after the start of the assessment process.

Assessment and appraisal process

• The timeframes for the assessment and appraisal process should be reviewed, so that the current time pressures at the end of the assessment report period and early appraisal period are reduced and more time allowed for critical evaluation of the consultees' comments. This does not necessarily mean that the overall timeline should be increased.

• The procedures for document management need to be carefully considered. This may include keeping some hard copy files of key documents for each Guidance, as well as the electronic files.

• NICE should improve interaction between Technical Assessment Groups, the NICE technical staff and the Appraisal Committee throughout the assessment and appraisal process. This could include, for example, having the continued involvement of the Technical Assessment Group as technical experts after the initial review of the appraisal consultation document.

Functions of the Appraisal Committee

• Given that a third Appraisal Committee is being introduced, NICE should take the opportunity to consider how to sustain the high quality performance of the Appraisal Committee. An issue that needs particular consideration is the question of consistency in decision-making across the three committees. NICE is already giving this question careful attention. Two possibilities to consider are: 1) having three individual Chairs and one common Vice-Chair; and 2) having the three Committees assess different types of technologies (e.g. diagnostic procedures for one and specific classes of pharmaceuticals for the other two).

• It should be made clear that membership of the Appraisal Committee is based on skills in and knowledge about evidence appraisal and judgement rather than on the representation of particular interests. Although that there is a need to ensure that manufacturers' views are taken into consideration, this should not be through membership of the Appraisal Committee but through the consultation process.

• The role of the Chair may need to be further refined. While it may be necessary for the Chair to continue to take an active role in leading the discussion on many items, the possible risks associated with this need to be carefully considered. Asking members to play a greater role in the ongoing review of a technology would allow the Chair to facilitate rather than lead the discussion, although the increased workload that would result for the Committee members would need to be assessed.

• NICE should assess whether the overall sustainability of the process and the functioning of the Appraisal Committee could be improved by the introduction of some type of reimbursement for members' time.

- The induction and training process for Appraisal Committee members needs to be further developed to include, where appropriate, enhancing skills in the critical appraisal of clinical evidence and economic evaluation.

- The Appraisal Committee procedures should be modified to ensure that a clear statement of what the Committee approves is recorded on the same day.

Decision-making

- NICE and the Appraisal Committee should continue their process to develop a system of decision-making that encourages articulation of the grounds for a particular recommendation, including specification of the weight that is placed on clinical evidence, economic evidence and other factors, such as equity and social values.

- As part of the process of articulating the criteria for decision-making, NICE must resolve the confusion related to the use of a value-for-money threshold. If a threshold is to be used as a basis for recommendations, it should be specified and justified for reasons of transparency.

- The Appraisal Committee may wish to consider having a legal advisor present during meetings, particularly those involving matters referred to the Committee by the Appeal Board.

Appeals

- In view of the considerable number of appeals lodged and their time and resource implications, thought needs to be given to how to reduce the number of appeals and the length of the appeal process. The further development of the appeal process will help enhance the quality and the transparency of the appraisal programme.

Budget impact and research

- Although budget impact is not a consideration in making recommendations on the use of a technology within the NHS, it is important to develop methods for budget impact modelling that would enable NICE to provide more detailed information on the implementation costs to the local authorities. This could be a task for the technical analysts in NICE. The advantages of doing so include not only the provision of useful advice to the Trusts, but also the avoidance of a duplication of effort by the Trusts in making their budget analyses for implementing the new technology.

- NICE should further develop the Research Required section of the Guidance and link it specifically with the review of Guidance review process. This would help to obtain the additional clinical evidence needed to ensure full understanding of the benefit of a technology. The Guidance review process would be an ideal way to stimulate the generation of such evidence.

- NICE should adopt more flexible timeframes for reviewing existing Guidance not only to ensure that the review answers a specific question but also to assist in managing workload. One approach might be for the set review dates to be dependent on the emergence of new evidence or significant changes in existing evidence.

Technical assessment report

- The contractual arrangement between the Technical Assessment Groups and the NCCHTA should be revised to recognize NICE as the primary client for the assessment reports.

- A handbook of standard methods for the assessment reports should be developed, after consultation between NICE staff, the Appraisal Committee and the Technical Assessment Groups. The handbook, which should be regularly updated, should also be used as the basis for training new reviewers and new NICE staff.

- A detailed template for the reports should be developed, including standardized data presentation and summary material. This would facilitate review of the information by the Appraisal Committee.

Input from the consultees

- On the basis of experience to date, NICE should consider what aspects of patient and professional submissions are most useful and develop standards for the content of these types of submissions.

- NICE should review the process for assessing comments from consultees and others (including the general public) that are submitted after the appraisal consultation document is drafted. NICE should determine the most appropriate way of responding to these inputs and assess their value in the decision-making process.

New advice on hormone replacement therapy

The Million Women Study has been carried out within the United Kingdom and involves around one million women aged 50 years of age and over. The main focus of the study relates to the effects of hormone replacement therapy use, but the large size of the study means that a very broad range of health issues were also investigated, including how various reproductive and lifestyle factors affect women's health, as well as diet, childbirth, breastfeeding, vitamin and mineral supplement use, oral contraceptive use and family history of illness. Results of the study were published in August 2003, and have provided new insights into the risks associated with hormone replacement therapy (HRT), in particular in relation to breast cancer(1).

The United Kingdom Committee on Safety of Medicine carefully reviews all new data on the safety of HRT. Other important information on the long-term risks of HRT — including coronary heart disease, stroke and ovarian cancer — was communicated in July 2002 following termination of one arm of the Women's Health Initiative (WHI) trial (2).

Summary table of risks and benefits associated with using HRT

Condition	Age of woman (yr)	Number of cases/1000 non-HRT users	Extra Number of cases in 1000 HRT users over the same period	
Cumulative cancer risk with time			5 years use	10 years use
Breast cancer	50–65	32	1.5 estrogen only 6 combined HRT	5 estrogen only 19 combined HRT
Endometrial cancer	50–64	5	4 estrogen only {no data} combined HRT	10 estrogen only <2 combined HRT
Ovarian cancer	50–69	9	1 estrogen only {no data}	3 estrogen only {no data}
Cardiovascular risks over 5 years				
Stroke VTE	50–59 60–69 50–59 60–69	3 11 3 8	1 4 4 9	{no data} {no data}
Benefits over 5 years			**Reduced number of cases in 1000 HRT users over the same period**	
Colorectal cancer Fracture of neck of femur	50–59 60–69 50–59 60–69	3 8 1–2 7–8	1 3 0–1 2–3	2 5–6 1 5

Findings of the Million Women Study showed that half the women had used HRT of which there had been 9364 incidents of breast cancer and 637 breast cancer deaths. Users of HRT were considered more likely to develop breast cancer but past users were not considered at increased risk. Incidence was significantly increased for current users of preparations containing estrogen only, estrogen-progestogen and tibolone, but associated risk for estrogen-progestogen was substantially greater than for other types of HRT. Ten years use of HRT is estimated to result in 19 additional cancers per 1000 users of estrogen-progestogen combinations. In conclusion, HRT causes a duration-dependent increase in the risk of breast cancer that begins to decline when HRT is stopped and by 5 years reaches the same level as in women who have never taken HRT.

The magnitude of the risk associated with estrogen-only products has been confirmed. For combined HRT use, the risk is significantly higher than with estrogen-only therapy. More specifically, the study demonstrates that:

- The increase in risk of breast cancer associated with combined HRT (relative risk RR = 2.00 compared with no use) is significantly higher than for estrogen-only therapy (RR = 1.30) and for tibolone (RR = 1.45).

- There is no evidence for a difference in risk of breast cancer between specific preparations or their route of administration within the classes of oestrogen-only therapy and any type of combined HRT.

- The estimated number of extra cases of breast cancer occurring after 5 and 10 years of using combined HRT were almost identical in the Million Women Study and the WHI trial.

The United Kingdom Committee on Safety of Medicine has issued the following advice to physicians and prescribers.

- For short-term use of HRT for the relief of menopausal symptoms, the benefits outweigh the risks for many women.

- For longer-term use of HRT, women must be made aware of the increased incidence of breast cancer and other adverse effects.

- Each decision to start HRT should be made on an individual basis and treatment should be regularly reappraised (at least once a year).

- For combined HRT the benefits of the lower risk of endometrial disorders, including cancer, should be weighed against the new information about the increased risk of breast cancer (see table). The risk of endometrial cancer with tibolone is not known.

- The results of the Million Women Study do not necessitate any urgent changes to women's treatment.

Summary

Hormone replacement therapy is an effective short-term treatment option for controlling symptoms of menopause. For each woman considering use of HRT, it is necessary that the benefits be weighed against the several risks that have been observed, including that of coronary heart disease within one year and breast cancer after one year of therapy.

Hormone replacement therapy should not be used for the long-term prevention of disease. For women currently taking long-term hormone replacement therapy for the treatment of osteoporosis, the risks now documented must be considered when reviewing individual circumstances as well as the consideration of the benefits and risks of alternative therapies.

For younger women with premature menopause or hypogonadism, the benefits of hormone replacement therapy would be expected to be greater and the risks probably smaller than those reported recently in the WHO study and Million Women Study (4).

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Direct-to-consumer advertising and patients

Direct-to-consumer advertising (DTCA) of prescription drugs has increased rapidly in the United States during the last decade, yet little is known about its effects on prescribing decisions in primary care.

From 1996 to 2000, spending on direct-to-consumer advertising (DTCA) of prescription drugs in the United States more than tripled (1), reaching US$2.7 billion in 2001 (2). The United States and New Zealand are the only industrialized countries that allow such advertising, although restrictive legislation in the European Union (3) and Canada (4) has recently been under review.

Canada allows advertising of over-the-counter (OTC) drugs but prohibits DTCA of prescription medicines, although a 1978 exemption, which was intended to allow price comparisons, permits advertising of product name, price and quantity (4). Nevertheless, Canadians see advertisements in US magazines and on US cable television, as well as an increasing volume of domestically generated DTCA of questionable legality (5). Proponents of DTCA argue that advertisements empower patients, whereas critics counter that they encourage wasteful prescribing (6).

A recent study has compared prescribing decisions in a US setting where DTCA is approved (Sacramento) and a Canadian setting where DTCA of prescription drugs is illegal (Vancouver) but some cross-border exposure occurs (7) .

The study showed that Sacramento patients were twice as likely to request medicines as patients in Vancouver and over twice as likely to request advertised drugs: request rates remained substantially different: 14.2% in Sacramento versus 8.8% in Vancouver. Advertising exposure was measured through the number of listed products a person had seen advertised, identification with an advertised condition, and use of advertising as an information source. In Sacramento, all 3 measures were associated with a higher probability of DTCA drug requests. In Vancouver, only the use of advertising as an information source (3.5% of patients) was significantly associated with DTCA drug requests.

Physicians fulfilled most requests for prescriptions in both settings: in Sacramento 80% of patients who requested prescriptions received them, as compared with 63% in Vancouver. The main difference was in the prescribing rate for requested nonadvertised drugs (81.4% v. 57.1%), although this difference was no longer statistically significant after adjusting for patient and physician characteristics. Prescribing rates for advertised drugs differed less: 77.6% v. 72.0%.

Sacramento patients reported more advertising exposure and requested more advertised drugs than patients in Vancouver and, in both settings, patients with higher exposure to advertising requested more advertised drugs. The prescribing rate for requested advertised drugs was similar, being about 75%.

Physicians judged 50% of prescriptions for requested DTCA drugs to be a “possible” or “unlikely” choice. A key argument made in favour of DTCA is that patients are protected because, ultimately, the physician decides whether or not to prescribe (8). However, if physicians prescribe products that they would not have chosen otherwise, the protection offered by prescription-only status is questionable. Also, patients do not obtain sufficient information from advertising to determine side effects and appropriateness (9). Indeed, many of the products requested were “lifestyle drugs” (10) or symptomatic treatments.

This survey opens an intriguing window on the effects of DTCA on patient–physician interactions in primary care. Results are consistent both with a dose-response to advertising at 2 different population exposure levels and, most importantly, with increasing industry investment in this marketing technique (2, 11). If DTCA opens a conversation between patients and physicians, that conversation is likely to end with a prescription despite frequent physician ambivalence about treatment choice.

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Action against counterfeit medicines in Asia and Africa

The World Health Organization (WHO) has launched an action plan against substandard and counterfeit medicines in six countries from the Greater Mekong sub-region. The plan follows similar initiatives begun in Africa and will continue to expand in response to countries' increasing call for assistance to improve the quality of their medicines.

Counterfeit and substandard medicines are frequently detected in Cambodia, China, the Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam and the problem seems to be increasing. Products most commonly counterfeited in this region include antibiotics and those used in the treatment of tuberculosis, malaria and HIV/AIDS. The use of poor quality or counterfeit medicines has little or no therapeutic effect and in poor settings may often lead to death.

At a meeting from 11–13 November 2003 in Hanoi, Viet Nam, WHO and the six countries will kick-start joint activities to combat counterfeiting of medicines in the region, to promote advocacy activities directed at key decision-makers, health professionals and the general public and to strengthen inspection and post-marketing surveillance.

Substandard medicines are thought to account for 8.5% of medicines on the market in Thailand. Eight per cent of randomly collected samples in Viet Nam and 16% in Myanmar failed laboratory testing for quality assessment. From these samples, rifampicin showed the highest failure rate at 26% followed by trimethorprim–sulfadoxine at 24%. In 2001, there were estimated to be over 2800 illegal medicine sellers in Cambodia and 1000 unregistered medicines on the market. In the Lao People's Democratic Republic, 2100 illegal drug sellers are said to exist.

With more complex combination medicines now being recommended for drug-resistant malaria, there is a strong possibility that more substandard and counterfeit medicines will enter the market in malaria-endemic countries. Even in terms of older, more traditional antimalarials, the quality of the medicines is often poor.

A recent WHO survey of the quality of antimalarials in seven African countries revealed that between 20% and 90% of the products failed quality testing. The antimalarials in question were chloroquine-based syrup and tablets, whose failure rate ranged from 23% to 38%; and sulfadoxine/pyrimethamine tablets, which showed 90% to be below standard. The medicines were a mixture of locally produced and imported products. Samples were submitted by Gabon, Ghana, Kenya, Mali, Mozambique, Sudan, and Zimbabwe.

Poorly equipped laboratories, under-funded regulatory authorities, poor handling and manufacturing practices were the main contributors to the presence of substandard and counterfeit medicines. Many tools exist to improve quality control of medicines and supply systems, but resources are lacking to support implementation. Most of the countries with the lowest quality pharmaceuticals are also the ones with the highest disease burden and the poorest economies.

The findings of the report have provided a basis from which to address potential problems in the transition to artemisinin-based medicines for drug-resistant malaria and has given impetus to the fight against poor quality and counterfeit medicines in Africa. WHO is now running a series of training workshops in several African countries to show manufacturers how to upgrade their standards, and show regulatory authorities how to improve practices in the screening and testing of local and imported products.

Reference: *WHO Press Release*, 11 November 2003. http://www.who.int

Essential Medicines

Neglected Diseases

The newly created **Drugs for Neglected Diseases Initiative** (DNDi) plans to spend around $250 million over the next 12 years to develop treatments to combat three killer diseases threatening a combined 350 million people every year: Chagas disease, sleeping sickness, and leishmaniasis. The DNDi is a not-for-profit association established in partnership with Médecins Sans Frontières, Oswaldo Cruz Foundation/Far Manguinhos, the Indian Council of Medical Research, Institut Pasteur, the Ministry of Health of Malaysia, and the Kenya Medical Research Institute, with WHO as a permanent observer.

The DNDi will identify opportunities and initiate and coordinate drug research and developmenrt (R&D) projects in collaboration with the international research community, the public sector, the pharmaceutical industry, and other relevant partners. In addition, the DNDi will support the implementation of research projects, including those in collaboration with South-South and North-South R&D networks.

The DNDi aims to build its R&D portfolio with drug discovery projects targeted at the identification of novel drug development candidates and drug development projects by taking candidate compounds through the different stages of development to the point where they can be registered and recommended for use. The DNDi website is available on: HTTP://www.dndi.org

Chagas disease

American trypanosomiasis, or Chagas disease, is a protozoan zoonotic disease caused by the haemoflagellate *Trypanosoma cruzi*, and is transmitted to humans either by blood-sucking triatomine vectors, blood transfusion or congenital transmission. This parasite infects over 150 species from 24 families of domestic and wild mammals, as well as humans. In the vertebrate host, *T. cruzi* infects many different cells, but in the human host, the disease is conspicuously limited to the myocardium and to gut nerve fibres.

Chagas disease is present in 18 countries on the American continent in two different ecological zones: the Southern Cone region, where the main vector lives inside human homes and in peridomiciliary areas; and Central America and Mexico where the main vector species lives both inside dwellings and in uninhabited areas. Country-wide crossectional surveys in the 1980s found an overall prevalence of 17 million cases, with 4.8–5.4 million people exhibiting clinical symptoms, an annual incidence of 700 000-800 000 new cases and 45 000 deaths due to the cardiac form of the disease.

Global distribution

Large-scale regional initiatives to halt vector-borne transmission and improved screening of blood-donors have been successful. At present, estimates indicate an infection prevalence of 13 million, with 3.0–3.3 million symptomatic cases and an annual incidence of 200 000 cases in 15 countries. The disease remains a priority health problem due to: the need for surveillance and control in areas where sylvatic vectors can invade dwellings; the medical and social costs of care for infected people in the absence of efficient and well-tolerated therapy, especially against the chronic form of the disease; the difficulty in obtaining priority for control activities and vector elimination in areas where vectorial transmission has been interrupted; and the need to continue strengthening mandatory blood-donor screening in endemic areas, as well as in non-endemic areas where increased travel and/or immigration of potentially infected donors might compromise donated blood supplies.

Developments

The complexity of the pathology of Chagas disease and the diversity of its clinical manifestations have made the understanding of its

pathogenesis difficult. The autoimmune hypothesis, once widely accepted, has increasingly been challenged by the parasite persistence hypothesis. Arguments for the latter hypothesis come from demonstrations of the presence of parasites in tissues of chronic patients, and the fact that treatments that decrease parasite burden are associated with a decrease in clinical symptoms. The two hypotheses might not be mutually exclusive since anti-immunopathogenic responses in chagasic patients might be driven by the parasite burden. Although further studies are needed, including elucidating the role of the recently described parasitokines, these results indicate an urgent need for the development of new antiparasite medicines, and their evaluation in large-scale randomized clinical trials, as well as for progress in the development of vaccines and immune interventions against pathogenesis.

New approaches for the characterization of *T. cruzi* and its vectors have been applied in laboratory, diagnostic, clinical and epidemiological studies, as well as in support of disease control. They have shed new light on the biology and genetics of these organisms, as well as on the genetics of the infected population, and strongly indicate that human infections are due to *T. cruzi* subgroup II. A possible breakthrough in clinical management of the chronic chagasic cardiomyopathy might involve the autologous transplantation of bone marrow cells into the circulation; patients with severe chagasic cardiomyopathy subjected to this therapy experienced improvement of the cardiac functions of up to 30%, in one case occurring one month after transplantation (17).

A Southern Cone initiative to eliminate the main vector, and interrupt transfusional transmission of *T. cruzi* was launched by the health ministries in Argentina, Bolivia, Brazil, Chile, Paraguay, and Uruguay in 1991. More than 2 500 000 houses were sprayed with insecticide between 1992–2001. Uruguay and Chile were declared free of vectorial transmission in 1997 and 1999, respectively, as were 9 of the endemic states of Brazil in 1990, and 4 endemic provinces of Argentina in 1991. Blood donor screening is mandatory in each of these countries. The extension of this model to Mexico, Central America, the Amazon and Andean Regions, however, will require adaptation and testing of vector control strategies to suit local epidemiological conditions.

Future prospects

The greatest risk to this improved trend in Chagas disease control comes from the success that has already been achieved, as the need for continued surveillance and selective interventions becomes less appreciated at the political level.

As the *T. cruzi* genome project nears completion, new approaches will become available for the identification and validation of new drug targets, early diagnostic indicators of infection and vaccine candidates, and for the elucidation of the mechanisms underlying host cell invasion, immune response and pathogenesis. The challenge will be to transform new knowledge into cost-effective, equitably affordable interventions and to guarantee their access to the patients and populations of endemic countries.

Regular updated information is available from the UNDP-World Bank-WHO Special Programme for Research and Training in Tropical Diseases (TDR) on http://www.who.int/tdr/dw/chagas2003.htm