WHO PHARMACEUTICALS NEWSLETTER

prepared in collaboration with the
WHO Collaborating Centre for
International Drug Monitoring,
Uppsala, Sweden

The aim of the Newsletter is to disseminate information on the safety and efficacy of pharmaceutical products, based on communications received from our network of "drug information officers" and other sources such as specialized bulletins and journals, as well as partners in WHO. The information is produced in the form of résumés in English, full texts of which may be obtained on request.

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No 1, 2009

This, the first issue for the year, brings you information on safety updates and regulatory decisions announced between late 2008 and mid-January 2009. We have also included the results of a survey conducted in 2006 by the WHO Collaborating Centre for Drug Statistics Methodology, Oslo, on the user community and applications of the ATC/DDD methodology.

We wish you all a very productive year in 2009 and thank you for your interest in the newsletter.

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Regulatory Matters

Safety of Medicines

Feature

Botulinum toxin type A

Possible risk of toxin spreading to distant parts of the body

Canada. Health Canada has issued safety update related to botulinum toxin type A products (BOTOX ®, BOTOX Cosmetic ®), about the risk of the toxin spreading to other distant parts of the body. Possible symptoms include muscle weakness, swallowing difficulties, pneumonia, speech disorders and breathing problems, and can be fatal. Health Canada says that it has worked with the manufacturer to revise the labelling of these products, noting that there are no medically confirmed cases of distant toxin spread in Canada. It also advises the public using the products to seek immediate medical care if swallowing, speech or breathing disorders arise.

Reference:
Advisories, Warnings and Recalls, Health Canada, 13 January 2009 (www.hc-sc.gc.ca).

Fentanyl transdermal patches

Changes to dosage conversion guideline

Canada. Manufacturers of all fentanyl transdermal patches have made changes to the dosage conversion guidelines and analgesic equivalency table of opioids in the Canadian Product Monographs for Fentanyl Transdermal Systems, according to Health Canada. With regard to the dosage conversion guidelines, the conversions from IM/IV morphine and IV hydromorphone to the fentanyl transdermal patch have been revised. In addition, the analgesic equivalency table has been revised to remove some data including those referring to IM meperidine, which is because the drug causes central nervous system toxicity if used by the parenteral route chronically. They also warned that serious or life-threatening hypoventilation can result if appropriate dose conversions are not used.

(See WHO Pharmaceuticals Newsletter No. 5 & 6, 2008 for adverse event reports following overdose with use of fentanyl patches in UK.)

Reference:
Advisories, Warnings and Recalls, Health Canada, 2 January 2009 (www.hc-sc.gc.ca).

Magnesium oxide

New warning about hypermagnesaemia

Japan. In September 2008, the Ministry of Health, Labour and Welfare (MHLW), Japan requested relevant pharmaceutical companies to amend the package inserts of magnesium oxide, to describe hypermagnesaemia and its initial symptoms in the "Clinically Significant Adverse Reactions" section, as well as to explain that serum magnesium levels should be periodically measured, especially when the drug is administered over long term. This action followed the review of 15 cases of hypermagnesaemia associated with magnesium oxide, including two fatal cases, reported to MHLW from April 2005 to August 2008. (Magnesium oxide is used as a laxative and as an antacid.)

Reference:
Pharmaceuticals and Medical Devices Safety Information No.252, November 2008, MHLW, Japan (www.pmda.go.jp/english/).

Nitrous oxide

Risk of neurological and haematological toxic effects

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) has alerted that prolonged use of nitrous oxide, a medical gas used widely in surgical anaesthesia, may lead in rare cases to megaloblastic anaemia and myelopathy due to inactivation of vitamin B12.

According to the Agency, neurological toxic effects occurred after a single exposure to nitrous oxide during general anaesthesia, in patients with vitamin B12 deficiency. Health-care professionals have been advised to consider assessment of vitamin B12 levels before nitrous oxide anaesthesia in people with risk factors for deficiency.

Reference:
Drug Safety Update, MHRA, Volume 2, Issue 5, December 2008 (www.mhra.gov.uk).

Oral sodium phosphate products

New alert on acute phosphate nephropathy

USA. The United States Food and Drug Administration (US FDA) issued an alert notifying health-care professionals and consumers of the risk of acute phosphate nephropathy associated with the use of oral sodium phosphate products (OSP) for bowel cleansing prior to colonoscopy or other procedures.

The US FDA is requiring the manufacturer of the two OSPs (Visicol and OsmoPrep), that are available by prescription only, to add a Boxed Warning to the labelling for these products, as well as to develop and implement

a risk evaluation and mitigation strategy (REMS), which will include a Medication Guide. The Agency recommends that in light of that risk, over-the-counter laxative OSP products should not be used for bowel cleansing.

Reference:
FDA Alert, US FDA, 11 December 2008 (*www.fda.gov*).

Rituximab and efalizumab

Risk of progressive multifocal leukoencephalopathy

UK (1). MHRA has issued safety advice about progressive multifocal leukoencephalopathy (PML) associated with the monoclonal antibodies rituximab and efalizumab. The Agency says that there have been reports of 76 cases of confirmed or suspected PML in patients treated with rituximab and two cases of PML in patients treated with efalizumab. Rituximab is indicated in combination with methotrexate for adults with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other antirheumatic drugs. Efalizumab is indicated for the treatment of adults with moderate to severe chronic plaque psoriasis who have failed to respond to, or are intolerant of, other systemic therapies.

The MHRA has advised that patients should be monitored regularly for neurological symptoms or signs that might suggest PML and that if PML is suspected, treatment must be suspended until PML has been excluded.

The Summaries of Product Characteristics are being updated.

Canada (2). Health-care professionals have been warned about the risk of serious infections, including PML, in patients receiving efalizumab (Raptiva). There have been reports of serious bacterial, viral, fungal and opportunistic infections, including two fatal cases in the United States of John Cunningham virus infection with PML in patients treated with efalizumab for plaque psoriasis, according to Health Canada. According to the Agency, if a patient develops a serious infection, efalizumab should be discontinued and appropriate treatment should be instituted.

The Canadian Product Monograph will be updated to include a boxed warning on the risk of serious infections, including PML.

(See WHO Pharmaceuticals Newsletter No. 5 & 6, 2008 for warnings of PML in the USA as well as reports on rituximab and efalizumab in VigiBase)

References:
(1). Drug Safety Update, MHRA, Volume 2, Issue 5, December 2008 (www.mhra.gov.uk).
(2). Advisories, Warnings and Recalls, Health Canada, 22 January 2009 (www.hc-sc.gc.ca).

Tacrolimus

Risk of serious medication errors

Netherlands (1). The Dutch Medicines Evaluation Board (MEB) has announced the receipt of reports of medication errors that could result in severe adverse events with the use of two products (Prograf and Advagraf) containing the immunosuppressant tacrolimus.

The marketing authorization holder has sent a letter to health-care professionals to draw their attention to the products' different dosing schedules: twice daily for immediate-release (Prograf) and once daily for prolonged-release (Advagraf).

UK (2). The MHRA has emphasized that the two products containing the immunosuppressant tacrolimus (Prograf and Advagraf) are not interchangeable and should not be substituted without careful therapeutic monitoring.

According the Agency, as of 10 December 2008, medication errors in prescribing, dispensing and administration with the two products (Advagraf and Prograf) have been reported in seven European (EU) countries and most reports were from the UK. Some of these errors have led to serious adverse reactions, including acute rejection of transplanted organs.

The Agency reminded health-care professionals of the correct dosing schedules for these products. Changes to the product information and labelling are planned to come into effect by April 2009.

References:
(1). News, Human Medicines, MEB, 10 December 2008 (www.cbg-meb.nl).
(2). Drug Safety Update, MHRA, Volume 2, Issue 6, January 2009 (www.mhra.gov.uk).

Toremifene

New contraindication in patients at risk of prolonged QT intervals

Europe. The European Medicines Agency (EMEA) has advised against the use of toremifene in patients at risk of prolonged QT intervals and other heart problems including electrolyte disturbances

(particularly hypokalaemia), clinically relevant bradycardia, clinically relevant heart failure with reduced left-ventricular ejection fraction, and a history of symptomatic arrhythmia. Toremifene is used to treat hormone-dependent metastatic breast cancer in postmenopausal women.

This recommendation is based on a review of toremifene by EMEA's Committee for Medicinal Products for Human Use (CHMP), which was conducted because of concerns that the medicine could cause QT prolongation. The CHMP has concluded that although the overall benefits of toremifene are greater than its risks, the use should not be allowed in patients with QT-prolongation or other heart problems. Additionally, it was recommended that toremifene should not be used together with other medicines known to prolong the QT-interval.

The EMEA is advising physicians to prescribe toremifene according to this updated product information.

References:

1. Press Release, EMEA, 22 January 2009 (www.emea.europa.eu).
2. Alert No. 120, Information Exchange System, WHO, 23 January 2009 (www.who.int/medicines).

Bevacizumab

Eye inflammation reported with unauthorized use

Canada. Health-care professionals have been informed of new safety information concerning off-label use of bevacizumab (Avastin) in the ophthalmology setting. Bevacizumab is authorized for intravenous administration in the treatment of patients with metastatic carcinoma of the colon or rectum in combination with fluoropyrimidine based chemotherapy.

The company says that it has been made aware of a number of cases of eye inflammation, endophthalmitis, blurred vision, and floaters, some of which are Toxic Anterior Segment Syndrome, in patients who were administered bevacizumab (Avastin) intravitreally.

It also says that in 2008, there was no unusual reporting pattern associated with bevacizumab (Avastin) distributed in Canada when used for the authorized indication.

***Reference**:*
Advisories, Warnings and Recalls, Health Canada, 16 December 2008 (www.hc-sc.gc.ca).

Herbal cold and flu products

Voluntary recall

Australia. Therapeutic Goods Administration (TGA), Australia has issued a health alert about voluntary recall of two herbal cold and flu medicines by the company, following reports of a number of allergic and anaphylactic reactions. Those products (Nyal Day & Night Cold & Flu Fighter tablets and Nyal Cold & Flu Fighter tablets) contain the herbs *Andrographis paniculata* (Andrographis), *Sambucus nigra* (Elderberry), *Salix alba* (White willow) and *Valeriana officinalis* (Valerian).

TGA has advised consumers using these products to stop their use immediately and to consult their doctor if they have concerns.

Reference:
Health alert, TGA, 19 December 2008 (www.tga.gov.au).

Icodextrin, intravenous immunoglobulins, galactose and d-xylose

Possible interference with non-glucose-specific glucose meters

Canada. Health Canada is warning about the possible interference of some medical products with certain blood glucose meters. According to the Agency, medical products which contain or are metabolised into maltose, galactose and xylose may induce falsely elevated blood glucose readings of non-glucose-specific glucose monitoring systems, because the enzymatic assays employed can react with those sugars. These products include, but are not limited to: intravenous immunoglobulins such as hepatitis B immune globulin injection, icodextrin peritoneal dialysis solution, galactose for tolerance test and d-xylose for tolerance test. Health Canada has received reports of falsely elevated glucose readings in patients with renal failure and who underwent icodextrin peritoneal dialysis. Health Canada has recommended using glucose-specific monitoring systems in hospitals.

(See WHO Pharmaceuticals Newsletter No. 5 & 6, 2008 for warning of interaction between icodextrin and glucose monitoring devices in the USA.)

Reference:
Advisories, Warnings and Recalls, Health Canada, 15 December 2008 (www.hc-sc.gc.ca).

Local anaesthetic with postoperative infusion pumps

Reports of articular chondrolysis

Canada. Health Canada has encouraged health-care professionals to refrain from using postoperative pain pumps for continuous intra-articular infusion of local anaesthetics, particularly with epinephrine, for pain management after shoulder surgery. Bupivacaine is commonly used with the pumps, and a combination of bupivacaine and epinephrine is also used, with the epinephrine inducing vasoconstriction and slowing down the absorption of bupivacaine.

As of July 2008, Health Canada received eight incident reports of articular chondrolysis following shoulder surgery that were suspected of being associated with the use of postoperative pain pumps. In these cases, all of the patients received bupivacaine with epinephrine.

Reference:
Canadian Adverse Reaction Newsletter, Health Canada, Volume 19, Issue 1, January 2009 (www.hc-sc.gc.ca).

Modafinil

Adverse skin and psychiatric reactions

Australia. The Australian Adverse Drug Reactions Advisory Committee (ADRAC) has received 10 reports with modafinil in Australia since 2003. The reports include two of skin reactions, five of serious psychiatric reactions, and three of gastrointestinal disturbance, rhinorrhoea and chest pain, respectively. Modafinil is used for the treatment of patients with excessive daytime sleepiness associated with narcolepsy or chronic shift work sleep disorder, and as adjunctive treatment in obstructive sleep apnoea/hypopnoea syndrome.

ADRAC has advised prescribers to exercise caution when prescribing modafinil to patients with a history of psychosis, depression or mania, and to discontinue modafinil at the first sign of rash or if patients experience psychiatric symptoms.

Reports in WHO Global ICSR database, Vigibase: Modafinil

Skin and appendages disorders: 209
Most reported reactions:
Pruritus 29
Rash 26
Stevens Johnson Syndrome 15
Sweating increased 21
Urticaria 22

Psychiatric disorders: 859
Most reported reactions:
Agitation 42
Anxiety 51
Confusion 42
Depression 45
Hallucination 40
Insomnia 59
Nervousness 60
Psychosis 39
Somnolence 71
Suicide attempt 63

(See WHO Pharmaceuticals Newsletters No. 1 and No. 2, 2008 for change to the product information in the UK and Canada, respectively).

Reference:
Australian Adverse Drug Reactions Bulletin, Volume 27, Number 6, December 2008 (www.tga.gov.au).

Natural health products

Update on adverse reactions

Canada. Health Canada has provided an update on adverse reactions reported for echinacea, ginkgo and St. John's wort, based on reports received by Health Canada from 1 July 2003 to 31 May 2008. The Agency previously discussed safety concerns regarding these products in the January 2004 issue of the *Canadian Adverse Reaction Newsletter.*

In addition, Health Canada has announced that it received 31 reports of adverse reactions suspected of being associated with valerian-containing products from 1 January 1990 to 31 May 2008. Of these 31 reports, 15 reports described psychiatric reactions such as visual hallucination, nightmares and abnormal thinking. Other reports include gastrointestinal disturbances, allergic reactions, increased hepatic enzyme levels and cardiac complications.

Reference:
Canadian Adverse Reaction Newsletter, Health Canada, Volume 19, Issue 1, January 2009 (www.hc-sc.gc.ca).

Temsirolimus

Severe hypersensitivity reactions during infusion

UK. The MHRA has given a warning about occurrence of hypersensitivity reactions with infusion of temsirolimus (Torisel), an antineoplastic agent used to treat patients with advanced renal-cell carcinoma. The reactions include flushing, chest pain, dyspnoea, hypotension, apnoea, loss of consciousness and anaphylaxis. According to the Agency, the marketing authorization holder had received 46 spontaneous reports of infusion-related hypersensitivity reactions, including one fatal outcome, until 3 April 2008.

The Agency has issued advice for health-care professionals regarding premedication (e.g. with diphenhydramine) of patients, dilution and administration of temsirolimus and other points for safe use.

(See WHO Pharmaceuticals Newsletter No. 4, 2008 for safety information in Canada).

Reference:
Drug Safety Update, MHRA, Volume 2, Issue 6, January 2009 (www.mhra.gov.uk).

Tinzaparin sodium injection

Increased risk of mortality in elderly patients

USA. The US FDA has issued a communication about its ongoing safety review of tinzaparin sodium injection (Innohep) (a low-molecular-weight heparin), recommending that health-care professionals should consider the use of

alternative treatments (to Innohep) when treating elderly patients over 70 years of age with renal insufficiency and deep vein thromboses, pulmonary emboli, or both.

In July 2008, the company revised the prescribing information to restrict the use of tinzaparin sodium injection (Innohep) in patients 90 years of age or older. According to the Agency, the preliminary data from the clinical study (Innohep in Renal Insufficiency Study), which was stopped in February 2008 because of an increase in all-cause mortality in patients who received the drug, suggest the increased risk of mortality is not limited only to patients 90 years of age or older. The US FDA has requested that the labelling for the product (Innohep) be revised to describe the overall study results which suggest that the drug increases the risk of death for elderly patients 70 years of age and older with renal insufficiency, compared to unfractionated heparin.

Conclusions and recommendations from the review of the final study report will be communicated to the public when completed.

Reference:
Communication about an Ongoing Safety Review, US FDA, 2 December 2008 (www.fda.gov).

Topical anaesthetics

Potential for serious, life-threatening adverse effects

USA. The US FDA issued a public health advisory to remind patients, health-care professionals and caregivers about potential hazards and the safe use of topical anaesthetics for relieving pain during mammography and other medical tests and conditions. The Agency has expressed concern about the potential for these drugs such as lidocaine to cause serious adverse effects when applied to a large area of skin or when the area of application is covered. It explains that if a topical anaesthetic is used improperly, the amount of the medication that reaches the blood stream is unpredictable and may be high enough to cause life-threatening adverse effects such as irregular heartbeat, seizures, breathing difficulties, coma and even death.

Before the issuance of this advisory, in February 2007, the US FDA issued a Public Health Advisory which described the deaths of two young women who used topical anaesthetics prior to laser hair removal.

Reference:
FDA News, US FDA, 16 January 2009 (www.fda.gov).

Varenicline

Serious neuropsychiatric events

Australia (1). According to ADRAC, there have been 339 adverse reaction reports with varenicline (Champix) until October 2008. Out of these, 225 (72%) describe psychiatric symptoms including depression, aggression, agitation, abnormal dreams, insomnia, hallucination and anger, as well as suicidal/self-injurious ideation or behaviour. Varenicline acts to relieve the cravings and withdrawal symptoms of smoking cessation and is used as an aid to stop smoking in adults.

ADRAC points out that an association between varenicline and serious neuropsychiatric events is increasingly likely. It has alerted prescribers, patients and family and carers about the possibility of such effects. In addition, prescribers have also been advised to be cautious when prescribing varenicline to patients with a history of seizure disorder, following 15 reports of seizures in patients using the drug.

Ireland (2). The Irish Medicines Board (IMB) notified the public of adverse reactions reported in association with the use of varenicline (Champix), including depression and suicidal ideation. Health-care professionals have been requested to be aware of the possible emergence of neuropsychiatric symptoms and to adhere to the approved recommendations for use of varenicline, as well as to advise patients of this risk.

Reports in WHO Global ICSR database, Vigibase:

Varenicline

Psychiatric disorders: 7746
Most reported reactions:
Aggressive reaction 565
Anxiety 539
Depression 929
Dreaming abnormal 429
Insomnia 466
Suicide attempt 726

References:
(1). Australian Adverse Drug Reactions Bulletin, Volume 27, Number 6, December 2008 (www.tga.gov.au).
(2). Notice Information, Irish Medicines Board, 5 January 2009 (www.imb.ie).

Weight loss pills

Warning about serious health risks

Switzerland (1). The Swiss Agency for Therapeutic Products (Swissmedic) has issued a warning regarding the serious health risks to the slimming product "Zhen de Shou Fat Loss Capsules", following the announcement of the US FDA that the product was placed on the US market illegally and sold via the Internet. The product contains sibutramine, for which a prescription is mandatory. The Agency says that taking this product can lead to numerous dangerous side effects such as high blood pressure or tachycardia, and even cardiac arrhythmia or stroke in patients with pre-existing heart conditions.

USA (2). The US FDA listed the names of 69 products marketed for weight loss that have not been approved by the Agency, and alerted consumers not to purchase or consume these products. They contain undeclared, active pharmaceutical ingredients that pose serious health risks (for example, high blood pressure, seizures, tachycardia, palpitations, heart attack or stroke), according to the Agency. These ingredients include sibutramine, rimonabant, phenytoin, phenolphthalein, bumetanide, and some of the amounts far exceed the US FDA-recommended levels.

The US FDA has advised consumers who have used the products to stop taking them and to consult their health-care professionals immediately. The Agency is seeking product recalls.

References:
(1). Announcements, Swissmedic, 12 December 2008 (www.swissmedic.ch).
(2). FDA News, US FDA, 22 December 2008 and 8 January 2009 (www.fda.gov).

Use of the ATC/DDD* methodology: an international survey

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Introduction
In 1995, the WHO Collaborating Centre for Drug Statistics Methodology (hereafter, the Centre) performed an international survey to know more about the types of users (Medicines Authorities, Industry and Researchers) and the different applications of the ATC/DDD methodology. Later, at the meeting of the International Working Group for Drug Statistics Methodology in October 2005, it was decided to update this information. In 2006, the Centre performed a new international survey in collaboration with the Working Group, the WHO Headquarters and the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA). The survey focused on the following:

- Organizations using the ATC/DDD methodology
- Reasons for using the methodology
- Coverage of ATC/DDD
- Usefulness of published ATC/DDD information
- Available drug catalogues/regulatory published drug utilization statistics

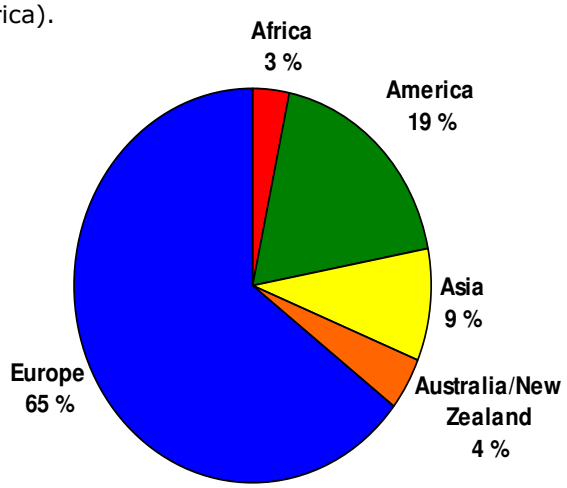
A summary of the survey is presented below.

Method
This was a web-based survey (Quest-Back). A questionnaire was distributed to approximately 900 e-mail addresses (876 successful e-mail deliveries) in over 100 countries.

Selection of participants
The complete mailing list was based on lists from
- the Centre (the e-mail distribution list of the Centre; main source),
- WHO HQ (the e-mail list for participants (180 e-mails) at the WHO International Conference of Drug Regulatory Authorities 2006),
- IFPMA (the main contacts and industry members in the IFPMA Health Care Systems working group).

Results
The overall response rate of the survey was 43 % (381 responders). Questionnaires were retrieved from responders in 65 % of the countries (i.e. 72 countries).
Figure 1 shows the response by region. 65 % of the responders were from the European region and 19 % from the Americas (North- and South-America).

Figure 1: Response by region

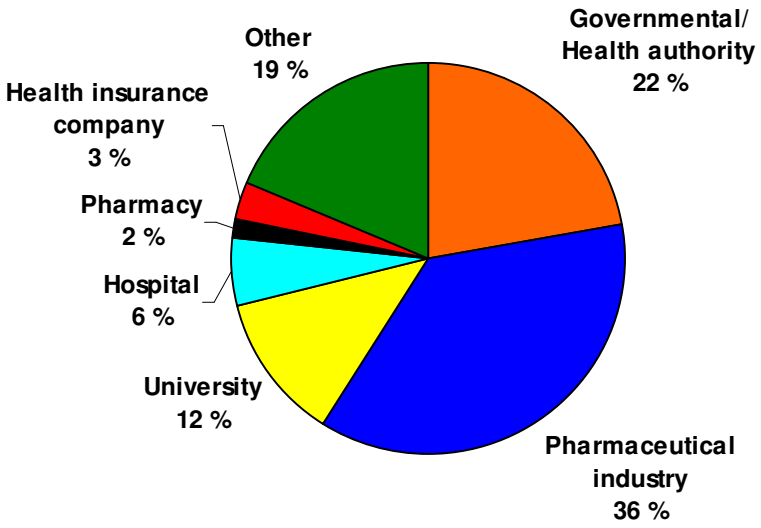


* ATC: Anatomical Therapeutic Chemical classification system; DDD: Defined Daily Dose

The response rate in Africa, America (North- and South-America) and Asia was approximately 38 %. The highest response rates were in Australia/New Zealand and Europe, 57 % and 44 %, respectively.

Figure 2 gives an overview of the categories of employment among the responders. Pharmaceutical industry accounted for 36 % of the responders, while health authorities/government represented 22 %.

Figure 2: Category of employment among the responders (response category)



ATC/DDD results

Figures 3, 4, and 5 show the feedback on the main questions concerning use of the ATC/DDD methodology.

Figure 3: Which parts of the ATC/DDD do you use?

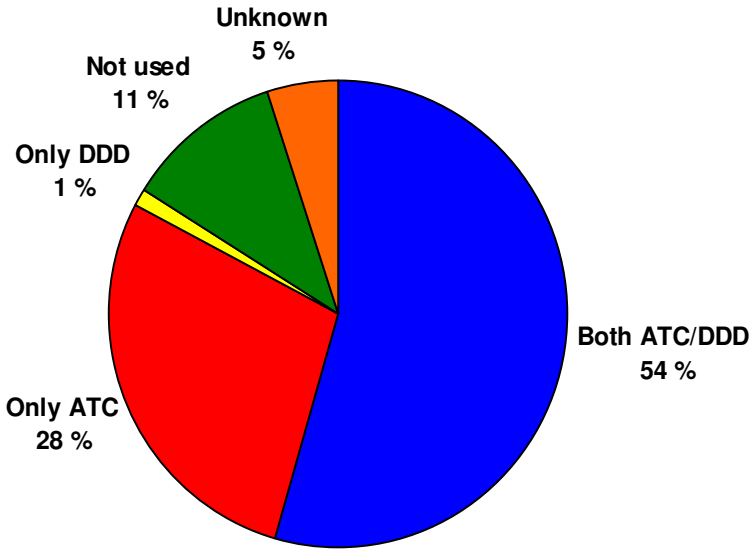


Figure 4: Which publications do you use?

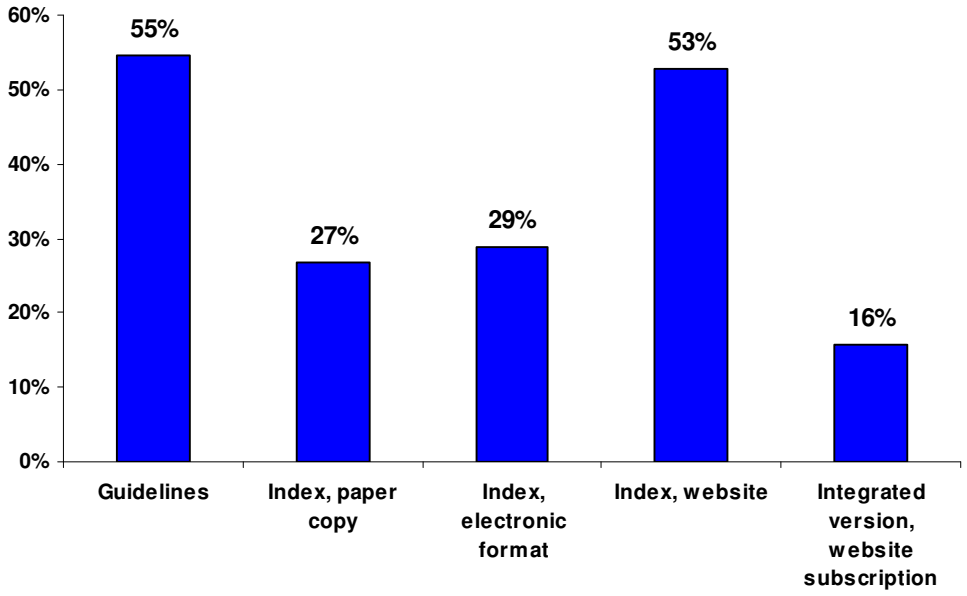
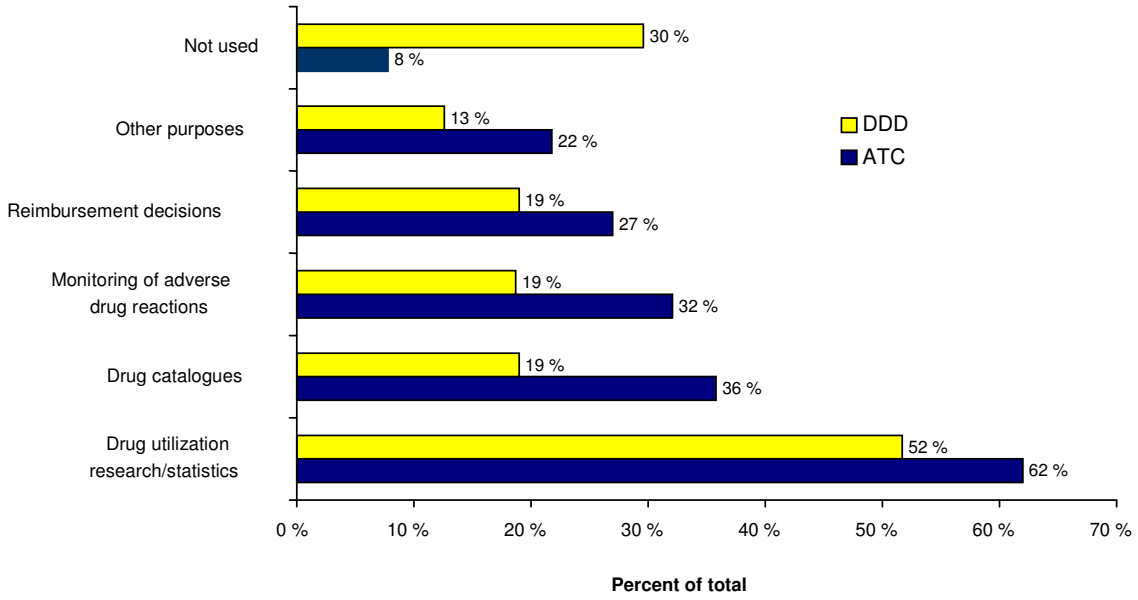


Figure 5: For what purpose(s) do you or your organisation/institute/company use the ATC classification and DDD methodology?



The responses to some of the other questions are summarized below:

- **Are ATC codes assigned for all medicines on the market in your country?**

50 % of the responders said yes, 20 % said they did not find codes for all medicines on the market, and 30 % did not know.

- **Do you find the DDDs you need in the ATC index?**

54 % said yes, 11 % said they did not find DDDs assigned for all medicines on the market, and 35 % did not know.

- **Do you find the Guidelines for ATC classification and DDD assignment useful?**

Responders found the guidelines *very* useful (44 %), useful (38 %), of limited use (6 %) or did not know (12 %)

- **Is the website of the WHO Centre (www.whocc.no) useful?**

33 % said the website was *very* useful, 41 % found it useful, 7 % that it was limited and 19 % did not know.

Discussion

A limitation of this survey is that it was very difficult to come up with a representative mailing list of possible users. The total response rate was 43 %. Sixty five per cent of the total number of responders in this study came from European countries (**fig. 1***)*. In this 2006 survey, the number of responders was the same as in 1995 from the African (11 vs 10) and Asian (34 vs 36) regions, but twice as many from the American region (72 vs 36 in 1995). Thus, the survey confirms that the ATC/DDD methodology is still most widely used in the European region (highest response rate). The survey did not draw equal number of responders from the different categories of employment. More than 50 % of the responders represented pharmaceutical industry or governmental/health authorities **(fig. 2**). 82 % of the responders used the ATC classification system, but 28 % said that they did not use DDDs. 54 % of the responders used both ATC and DDD. Only 1 % of the users indicated that they used DDD only (**fig. 3).** The survey confirms that all the Centre's publications are being used (**fig. 4**). The web application of the Index seems to cover a need. More people use the ATC Index than the Guidelines.

The question "**For what purpose(s) do you or your organisation/institute/company use the ATC classification and DDD methodology?**" was included both in the 1995 and 2006 surveys. It is now clear that more than half of the responders use ATC and DDD according to its main purpose: as a tool for drug utilisation research. 36 % responded that they used ATC in drug catalogues (compared to 44 % in 1995). Since ATC/DDD is an international language, use of ATC in drug catalogues is considered important and such use is encouraged.

Basing detailed reimbursement, therapeutic group reference pricing and other specific pricing decisions on the ATC and DDD assignments is a misuse of the system (reference: *Guidelines for ATC classification and DDD assignment, 2009*). Results from the survey indicate that such use does occur; however, the relative response is very similar to the 1995 figures.

It is a fact that ATC codes and DDDs are not established for all medicines marketed around the world. Half of the responders confirmed that ATC codes were assigned for all medicines in their respective countries. More than half of the users found the DDDs they needed. It is important to remember that the WHO Centre in Oslo establishes new entries in the ATC classification on requests from the users of the system. Thus, the Centre is encouraging all users to apply for new ATC codes and DDDs when needed. Further, it should be taken into consideration that complementary (e.g. homeopathic preparations) and traditional medicinal products (e.g. herbal remedies) are in general not included in the ATC system and that in some ATC groups, no DDDs are assigned because of highly individual use and wide dose ranges (e.g. in ATC group D (Dermatologicals) and L01 (Antineoplastic agents)). The survey confirmed that the users of the ATC/DDD system consider both the Guidelines and the website useful.

Conclusions

The survey indicates that the ATC/DDD system is appreciated by the users. The Centre has, however, received comments, advices and recommendations to improve the applicability of the system which will be further investigated. The website of the Centre is extensively used, and as a result of this study the Centre will give priority to the task of improving its website. Finally, attention should be drawn to the fact that some parts of this survey are difficult to interpret, and this has to be taken into consideration when reading this summary. The Centre would like to take this opportunity to thank all of the responders for their feedback in this survey.

In the WHO Pharmaceuticals Newsletter No. 3, 2008 pp. 10-12, we published a report from the WHO Collaborating Centre for International Drug Monitoring entitled "**Review of Oseltamivir Reports in Vigibase is reassuring but vigilance for hepatic and skin disorders recommended**". The intention of the review was to ascertain whether there were signals of serious adverse reactions with this medicine in Vigibase that were not already documented in the literature or product information. At this time serious neuropsychiatric reactions had already been identified and this was stated in the text.

It has been brought to our attention that the title of the article has the potential to be misleading as it does not refer to the serious neuropsychiatric reactions that have been observed with this medicine. The author of the article has acknowledged this omission and wishes to apologize for any confusion that may have been caused by the title.