WHO Drug Information

Contents

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Contents *(continued)*

International Nonproprietary Names

Nomenclature for monoclonal antibodies

In October 2008, the World Health Organization's (WHO) Programme on International Nonproprietary Names (INN) convened a Working Group meeting to discuss nomenclature for monoclonal antibodies (mAbs). The objective of the meeting was to review the current situation in light of the challenges highlighted during the 46th Consultation on International Nonproprietary Names (INNs) for Pharmaceutical Substances in April 2008 (1, 2). The Working Group focused on drafting recommendations for any necessary modifications to the system to facilitate development of INNs for mAbs. A report from that meeting has now been published and is summarized below.

The first INN for a monoclonal antibody (mAb), muromonab CD3, was adopted twenty years ago. Following this, the stem –mab was proposed and adopted for all new INNs for mAbs. Between 1991 and 1993, the basis of the INN system for mAbs was devised with the first infixes for source and target of antibodies being formulated. Since 1998, 173 mAb INNs have been published and this class of products now represents a significant proportion of the total number of INNs for biologicals. This period also saw a move away from rodent-sequence mAbs to humanized or human mAbs.

Requirements for INNs for mAbs
INNs for mAbs must be unique and unrelated to trade names/trademarks. They must be distinct and transposable into several languages. They need to be convenient for users and it is preferable that they be limited to no more than three or four syllables. INNs are intended to provide information concerning mAbs to scientists, physicians, pharmacists and other interested parties.

The linguistics concerning INNs for mAbs can be very problematic. Many groups of INNs appear "overcrowded" and many have similarities in look or sound. This situation is made more complex by the need to include systems for pegylated mAbs and for radiolabelled mAbs. Additionally, mAb conjugates use a second word for the non-mAb part.

The length and complexity of the words and stems has led to clumsy, long INNs when compared to INNs for other classes of biologicals and chemicals and the need to adopt INNs for an ever increasing number of mAb products is causing INNs to become ever longer. At present 52 names have 4 syllables, 99 have 5 syllables and 5 have 6 syllables and this trend towards very long names is increasing. The clinical success rate for mAbs is relatively low compared with other products, which results in many adopted INNs finally remaining unused, at least as names for approved products.

Usage, stems and sub-stems
The stem -mab is well accepted and recognized as indicating a mAb. However, several antibody products are fragments, such as Fab or F(ab')2 while a range of other types of fragments (e.g., minibodies) are being developed. It would be possible to adopt new stems for these, e.g., -fab, but this would cause confusion since several Fab fragments have already been given an INN with the -mab stem. It is also unclear if -fab would be used for all fragments or whether further stems would also need to be adopted.

Sub-stems (infixes) which indicate species sequence/structure of mAbs are widely understood and used. They may also include some information on how the mAb may have been produced. Four such sub-stems, -zu-,-o-,-u-,-xi- (humanized, mouse, human and chimeric) have been used, but some e.g., -e- and -i- (hamster and primate mAbs), have never been used. Nonetheless, it is possible that this could change in the future: for example, there is current interest in some primate antibodies. It has been proposed to discontinue the use of sub-stems and replace them with syllables indicating the specific targets of the mAbs. However, this would cause discontinuity with existing INNs and ignores any need to consider the species origin of the sequence of mAbs.

Sub-stems for disease/target are less well known. The target sub-stems -li- (immunomodulatory) and -tu- (tumour) have been used mostly: 48 as -li(m)- and 50 as -tu(m)-, followed by -vi(r)-. Others have much lower usage. Specific tumour sub-stems (other than -tu(m)-) have been little used and some have never been used. In many cases it is possible to select more than one sub-stem for a particular mAb. It may be necessary to introduce new target-related sub-stems for some types of antibodies such as bispecific mAbs.

Post-translational modifications and implications for INNs

MAbs undergo post-translational modifications which are dependent on the expression system used for production. Most of these do not significantly affect clinical use but some can influence pharmacokinetics and/or immunobiological functions. In particular, glycosylation can, in some cases, be necessary for optimal clinical activity. Nearly all mAbs are glycosylated and show expression system and production process related glycan structures. Glycosylation sites are present in the Fc region and sometimes also in the Fab part of the mAb. Differences in glycosylation of mAbs can be introduced deliberately (by glycoengineering) or occur unintentionally because of differences in manufacturing processes. Products are ‘mixtures’ containing different glycoforms and are not all of one homogeneous glycoprotein structure. Different batches of a product can vary in microheterogeneity and, in addition, modification to production processes can result in changes in glycosylation pattern (and other post-translational modifications). Significant clinical effects of glycosylation may need to be reflected in INNs.

Although most mAbs are glycosylated, their INNs have not been given terminal Greek letters as has been done for some other glycoproteins (e.g., hormones). The possibility exists that two or more mAbs could be produced which have the same amino acid sequence, but differ in glycosylation. To introduce terminal Greek letters for all new INNs could cause confusion and discontinuity with existing INNs.

At present all existing INNs for mAbs relate to mAbs with different amino acid sequences. If future INN applications are received for mAbs with the same sequence as an existing mAb, but different glycosylation, the INN for the latter application could be the existing INN but with a terminal beta added. Subsequent Greek letters could be used for further INNs for mAbs with this antibody sequence, as for other glycoproteins. Concern was also raised that the use of Greek letters to denote any difference in glycosylation could lead to product specific INNs which would undermine the nonproprietary nature of the INN. Nevertheless, this is consistent with the INN policy for recombinant DNA derived proteins.

Definitions

The INN cannot possibly fully describe all the characteristics of a mAb. The descrip-

tion/definition should be the source of detailed information concerning the mAb. Definitions are very important but some are very complicated and detailed. They should consist of two parts, one general and easy to follow and the other more detailed. The definition is linked to the amino acid sequence.

Applicants will need to be asked to provide the required information for the definition as well as details on glycosylation, etc. The details of the type of information needed are available on the INN application form and the correct amino acid sequence must be stated. The clone name should also be included but not in the general definition. If mAbs contain a glycosylation site, then they will normally be glycosylated. If the mAb is glycoengineered this should be indicated in the definition.

General policies for monoclonal antibodies

- INNs for monoclonal antibodies (mAbs) are composed of a prefix, a substem A, a substem B and a suffix.
- The common stem for mAbs is -mab, placed as a suffix.
- The stem -mab is to be used for all products containing an immunoglobulin variable domain which binds to a defined target.

Sub-stem B indicates the species on which the immunoglobulin sequence of the mAb is based:

a		rat
axo	(pre-sub-stem)	rat/mouse
e		hamster
i		primate
o		mouse
u		human
xi		chimeric
-xizu-	(under discussion)	chimeric/humanized
zu		humanized

The distinction between chimeric and humanized antibodies is as follows:

A ***chimeric*** antibody is one that contains contiguous foreign-derived amino acids comprising the entire variable domain of both heavy and light chains linked to heavy and light constant regions of human origin.

A ***humanized*** antibody has segments of foreign-derived amino acids interspersed among variable domain segments of human-derived amino acid residues and the humanized variable heavy and variable light domains are linked to heavy and light constant regions of human origin.

The -xizu- infix is used for an antibody having both chimeric and humanized chains.

The -axo- infix is used for an antibody having both rat and mouse chains.

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General policies for monoclonal antibodies *(continued)*

Sub-stem A indicates the target (molecule, cell, organ) class:

-b(a)-	bacterial
-c(i)-	cardiovascular
-f(u)-	fungal
-k(i)-	interleukin
-l(i)-	immunomodulating
-n(e)- (under discussion)	neural
-s(o)-	bone
-tox(a)	toxin
t(u)	tumour
-v(i)-	viral

In principle, a single letter, e.g., -b- for bacterial, is used as substem A. Whenever substem B starts with a consonant (e.g., x or z), an additional vowel indicated in the table, e.g., -ba-, is inserted to avoid problems in pronunciation.

Prefix
The prefix should be random, e.g., the only requirement is to contribute to a euphonious and distinctive name.

Second word
If the product is radiolabelled or conjugated to another chemical, identification of this conjugate is accomplished by use of a separate, second word or acceptable chemical designation. For instance, for mAbs conjugated to a toxin, the suffix -tox can be used in the second word.

If the monoclonal antibody is used as a carrier for a radio-isotope, the latter will be listed first in the INN, e.g., technetium (99mTc) nofetumomab merpentan (81).

The prefix peg- can be used for pegylated mAbs, but this should be avoided if it leads to over-long INNs. In most cases, it is best to adopt two-word INNs for pegylated mAbs, with the first word describing the mAb and the second being pegol or a related designation.

Other matters
Information relating to details of structure (which must be provided by the manufacturer/applicant) is crucial for deciding on an appropriate INN. It is up to manufacturers to approach WHO for an INN and regulators should request companies to apply for an INN. They are also responsible for checking and validating if an INN is correctly used and corresponds to the substance which is the subject of a Marketing Authorization.

Companies should apply for an INN when clinical evaluation begins. INNs are needed for a product at this stage because an alternative means of identification, e.g., using manufacturer codes, is very confusing.

Many mAbs fail at phase III trials. This is late in the evaluation process when they will almost certainly have received an INN. This accounts for the many INNs which exist for clinically failed mAbs.

Recommendations

The present system needs modification, revision and improvement to deal with specific problems. However, it has been used successfully for twenty years and changes should be carefully considered and implemented only where necessary. The following proposals have been highlighted in particular:

- The stem -mab should be retained. Also -mab is to continue to be used for mAb fragments. The description should clearly indicate if the product is a fragment.

- The system for conjugates and radiolabelled mAbs need not be changed.

- The stem -mab is to be used for all products containing an immunoglobulin variable domain which binds to a defined target.

- The prefix peg- can be used for pegylated mAbs, but this should be avoided if it leads to an over-long INN. In most cases, it is best to adopt two-word INNs for pegylated mAbs, with the first word describing the mAb and the second being pegol. This is consistent with INNs for other pegylated substances.

- The use of sub-stems is valuable but possibly too complicated. The 'source' sub-stem should be kept but redefined as 'the species on which the immunoglobulin sequence of the mAb is based'. The 'tumour group' sub-stem should be simplified to -tu(m)-, the other tumour sub-stems should be discontinued. But -tu(m)- should be truncated to -t- or -tu-. Similarly -li(m)- should be truncated to -m- or discontinued and replaced with more precise sub-stems, which relate to the target. Also the other sub-stems for 'disease or target' should be shortened, e.g., -fung- to -f-.

- The use of Greek terminal letters to indicate differences in glycosylation cannot be introduced retrospectively. However, mAbs which have the same amino acid sequence but different glycosylation may need distinct INNs unless significant differences on post-translational modifications are excluded/misproven. In particular, if the glycosylation has been glycoengineered to produce a different structure, then the glycoengineered mAb should be given a different INN to the parent mAb.

- When the antibody is directed against a toxin, the infix -toxa- can be used in the name. For monoclonals conjugated to a toxin, the suffix -tox can be used in the second word. This will be clarified in the mAb naming rules.

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Safety and Efficacy Issues

Mycophenolate mofetil: pure red cell aplasia

Canada — The manufacturer of mycophenolate mofetil (CellCept®) has provided new safety information on reports of pure red cell aplasia (PRCA). Mycophenolate mofetil is an immunosuppressive agent indicated for the prophylaxis of acute transplant rejection in adults receiving allogeneic renal, cardiac or hepatic transplants, and in children and adolescents (2–18 years) receiving renal transplants. Mycophenolate mofetil should be used concomitantly with cyclosporine and corticosteroids.

The mechanism for mycophenolate mofetil induced PRCA is unknown. In some cases, PRCA was found to be reversible with dose reduction or cessation of therapy. In transplant patients, however, reduced immunosuppression may place the graft at risk. PRCA is usually treated by attending to the underlying condition (disease) or discontinuing the drug that causes PRCA.

PRCA is a type of anaemia that develops secondary to failure of erythropoiesis. Erythropoiesis is a process by which red blood cells (RBCs) are produced from immature precursors in the bone marrow. PRCA describes a condition in which RBC precursors in bone marrow are nearly absent, while megakaryocytes and white blood cell precursors are usually present at normal levels. PRCA may be idiopathic or occur as a manifestation of an underlying condition. Approximately 5% of all cases of PRCA are drug induced. Patients with PRCA may present with fatigue, lethargy, and/or abnormal paleness of the skin. Anaemia is the primary clinical concern in PRCA. The degree of anaemia can range from subclinical to severe.

As of 24 February 2008, 41 cases of PRCA have been reported in patients receiving mycophenolate mofetil in combination with other immunosuppressive agents (tacrolimus, cyclosporine, corticosteroids, azathioprine, sirolimus and alemtuzumab).

Reference: Communication dated 3 June 2009 from Hoffmann-La Roche Limited posted on the Health Canada site at http://www.hc-sc.gc.ca

Swine flu ADR portal

United Kingdom — Oseltamivir (Tamiflu®) and zanamivir (Relenza®) have been stockpiled for management of the swine flu pandemic. In order to efficiently monitor the safety of oseltamivir and zanamivir as their use increases, a special web-based system for reporting suspected ADRs to these medicines – the Swine Flu ADR Portal — has been set up.

This is available at www.mhra.gov.uk/swineflu and will remain in operation for the duration of the pandemic. The portal has been designed to make completing a report as quick and easy as possible. When H1N1 swine flu vaccines become available in the Autumn, the portal should also be used to report suspected ADRs to these vaccines.

The Swine Flu ADR Portal will be open to members of the public as well as health care professionals.

Reference: MHRA. Swine flu - Reporting suspected adverse reactions to Tamiflu®, Relenza® and future Swine flu H1N1 vaccines. http://www.mhra.gov.uk/

Propylthiouracil: serious liver injury

United States of America — The Food and Drug Administration (FDA) has warned health care professionals of the risk of serious liver injury associated with the use of propylthiouracil for the treatment of Graves disease.

Propylthiouracil was approved for marketing in 1947. A total of 32 cases of serious liver injury associated with the use of propylthiouracil were reported to the FDA's Adverse Event Reporting System since that system was established in 1969 through October 2008. Of the 22 adult cases, the FDA identified 12 deaths and five liver transplants. Of the 10 paediatric cases, there was one death and six reports of liver transplant.

Propylthiouracil is considered second-line drug therapy except in certain patients who are allergic or intolerant of methimazole. Because a rare birth defect has been reported with methimazole and not with propylthiouracil, propylthiouracil may be more appropriate for patients with Graves disease who are in the first trimester of pregnancy.

Reference: *FDA News Release*, 3 June 2009 at http://www.fda.gov

Fosamprenavir: myocardial infarction

Canada — The manufacturer of fosamprenavir (Telzir®) has informed healthcare professionals of important safety information regarding a potential association between myocardial infarction and exposure to fosamprenavir in HIV-infected patients. Fosamprenavir is a protease inhibitor (PI) used in combination with low-dose ritonavir and other antiretrovirals in the treatment of HIV-1 infection.

A nested case-control study conducted in the French Hospital Database on HIV has reported an association between exposure to fosamprenavir and an increased risk of myocardial infarction. This may be related to the propensity for this drug class to raise blood lipids. Triglyceride and cholesterol levels should therefore be checked prior to initiating therapy with fosamprenavir and at periodic intervals during therapy. Other modifiable risk factors for cardiovascular disease (such as hypertension, diabetes and smoking) should also be monitored in HIV-infected subjects and managed as clinically appropriate.

Recent data presented at the 16th Conference on Retroviruses and Opportunistic Infections suggested a potential association between fosamprenavir and myocardial infarction in HIV infected adults. The nested case-control study reported an increased risk of myocardial infarction in association with cumulative exposure to fosamprenavir. Myocardial infarction has already been identified as being potentially associated with the PI class in the ongoing Data Collection on Adverse Events of Anti-HIV Drugs (DAD).

Suppression of viral replication in HIV disease with antiretroviral therapy is of the utmost importance. Physicians should monitor a patient's cardiovascular risk as part of the follow-up and seek to adjust modifiable risk factors. Combination antiretroviral therapy is associated with redistribution of body fat (lipodystrophy) in HIV-infected patients. Clinical examination should include evaluation for physical signs of fat distribution. HIV infection itself has been associated with lipid disorders and ischaemic heart disease.

Reference: Communication from the manufacturer dated 17 July 2009 at http://www.hc-sc.gc.ca

TNF inhibitors and lupus erythematosus: an emerging association

Australia — Systemic lupus erythematosus (SLE) is considered drug-induced when, in relation to a suspect drug, both of the following apply:

- Idiopathic lupus features or antibodies are absent prior to treatment.
- Recovery occurs within one year of withdrawal of treatment.

Clinically, drug-induced lupus erythematosus (DILE) tends to be similar to and less severe than idiopathic SLE: arthralgia, myalgia and skin rash (not the classic malar rash) are prominent, renal or neurological involvement is rare. Management requires withdrawal of the suspect drug, after which improvement begins, generally within weeks. Arthralgia/arthritis may call for treatment with an NSAID, and severe symptoms may require short courses of corticosteroids (1).

Tumour necrosis factor (TNF) inhibitors (infliximab, adalimumab, etanercept) are powerful immunosuppressants approved for indications including rheumatoid and psoriatic arthritis, ankylosing spondylitis, and Crohn disease. However, the deficiency of TNF caused by these drugs is known to predispose some patients to TNF inhibitor-induced SLE.

In clinical studies of rheumatoid arthritis, two of 3000 adalimumab-treated patients developed new-onset lupus-like syndrome, remitting on withdrawal of adalimumab (2). There are also case reports of DILE in association with adalimumab, etanercept and infliximab (3, 4).

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 28, Number 3, June 2009 at http://www.tga.gov.au/adr/aadrb/aadr0906.htm#a1

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Triamcinolone acetonide: serious ocular reactions

Canada —Triamcinolone acetonide is a synthetic corticosteroid primarily used for its marked anti-inflammatory action (1). It was authorized for use in Canada as a 10-mg/mL suspension (Kenalog-10®) in 1966, and as a 40-mg/mL suspension (Kenalog-40®) in 1973. Currently, generic products are also available. In Canada, the 40-mg/mL suspension has been authorized for intramuscular and intra-articular administration or for injection into tendon sheaths or ganglia. It is indicated for systemic corticosteroid therapy in conditions such as dermatoses or rheumatoid arthritis and other connective tissue disorders (1).

Intravitreal or intra-ocular injection of this product is not an authorized route of administration in Canada. Diabetic macular edema, cystoid macular edema and choroidal neovascularization secondary to age-related macular degeneration are among the conditions for which the use of intravitreal injection of triamcinolone has been reported (2, 3). In 2007, a safety notice was published in France regarding the occurrence of serious ocular adverse reactions (ARs) following intravitreal injections of the 40-mg/mL suspension (4).

Topical ophthalmic, oral and intravenous corticosteroids have long been associated with ocular ARs. Local injections of corticosteroids, even at sites far from the eye, have been associated with eye complications such as the development of cataract, glaucoma, and even retinal and choroidal emboli (5).

Intravitreal injection of triamcinolone has several reported complications including retinal detachment and vitreous haemorrhage. Complications developing later include cataract progression, steroid-induced glaucoma and endophthalmitis (2). Triamcinolone persists for long periods. Low concentrations were found in samples of aqueous humor up to 1.5 years after intravitreal injection (6). Cases of increased intraocular pressure requiring medical intervention following intravitreal injection have also been reported. Patients with a history of primary open-angle glaucoma are at a higher risk of increased intra-ocular pressure (2).

A number of ocular ARs following intravitreal injection of triamcinolone in Canada have been reported in the scientific literature (2). They included increased intraocular pressure requiring glaucoma medication (60 cases), cataract progression requiring extraction (12), endophthalmitis (1) and temporary occlusion of the central retinal artery (1).

Extracted from Canadian Adverse Reactions Newsletter, volume 19, issue 3, july 2009 at http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v19n3-eng.php

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Safety updates on insulin glargine

European Union — The European Medicines Agency (EMEA) is looking into four recently published registry studies investigating a possible relationship between insulin analogues, in particular insulin glargine, and the risk of cancer. The studies were published on the *Diabetologia* website on 26 June 2009.

Insulin glargine is a long-acting insulin analogue, authorized in the European Union (EU) as Lantus® and Optisulin®, for the treatment of adults, adolescents and children aged six years or above with diabetes when treatment with insulin is required.

The results of the four studies were found to be inconsistent. In two studies (Scottish Diabetes Research Network Epidemiology Group and Jonasson et al) an association between breast cancer was found in a group of patients taking insulin glargine as monotherapy, but not in another group of patients using insulin glargine together with other types of insulin. For other cancers, no association was found. In these two studies, dose-dependency was not evaluated. The third study (Hemkens et al) reported a dose-

dependent association between use of insulin glargine and malignancies. However, no information is available on the types of cancer found in this study. In the fourth study (Currie et al), no association between cancer (either breast, colorectal, pancreatic or prostate cancer) and the use of insulin glargine, or any other insulin, was found.

On the basis of currently available data, a relationship between insulin glargine and cancer cannot be confirmed nor excluded. However, concerns raised by the four studies require further in-depth evaluation (1).

The Committee for Medicinal Products for Human Use (CHMP) has since carried out an in-depth review of four studies and their outcomes. Due to methodological limitations the studies were found to be inconclusive and did not allow a relationship between insulin glargine and cancer to be confirmed or excluded. In addition, the Committee noted that the results of the studies were not consistent.

Because of the limitations of the existing evidence, the Committee has requested the marketing authorization holder to develop a strategy for generation of further research in this area. In addition the Committee is exploring possibilities for cooperation with academia to generate further information.

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Fentanyl transdermal patches and accidental child exposure

Canada — The fentanyl transdermal system is indicated in the management of persistent, moderate to severe chronic pain that cannot be managed by other means such as opioid combination products or immediate-release opioids (1). The system has been marketed in Canada under the brand name Duragesic® since 1992. In 2006, the generic products Ratio-Fentanyl® and Ran-Fentanyl® transdermal systems were introduced.

Safety of the fentanyl transdermal system is contingent on its use according to the conditions recommended in the Canadian product monographs. The warnings and precautions section of the monographs have been updated to include accidental exposure. Examples of accidental exposure include the transfer of a fentanyl transdermal patch while hugging, sharing a bed or moving a patient (1–3).

In December 2008, Health Canada received a report of suspected accidental fentanyl exposure in a healthy 19-month-old child. He was sleeping in the same bed as his mother, who was using a fentanyl patch for chronic pain. The patch inadvertently became attached to the child. He was taken to hospital and given naloxone 0.01mg/kg intramuscularly as required. The child was monitored overnight, and his condition improved after treatment (1–4).

Extracted from Canadian Adverse Reactions Newsletter, volume 19, issue 3, july 2009 at http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v19n3-eng.php

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Clopidogrel interactions with proton pump inhibitors

United Kingdom — The European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) has recently considered the available evidence for an interaction between clopidogrel and proton pump inhibitors (PPIs). They concluded that PPIs reduce the effectiveness of clopidogrel in preventing the recurrence of adverse cardiac events such as heart attack and coronary artery restenosis.

Clopidogrel (Plavix®) is used to prevent atherothrombotic events in patients who have previously had one of these events, or in at-risk patients who have peripheral arterial disease. In combination with aspirin, it can also be used to prevent atherothrombotic events in patients with acute coronary syndrome.

PPIs are used to treat gastrointestinal disorders, oesophageal reflux disease , dyspepsia or gastric ulcers. In the United Kingdom, five PPIs are available on prescription: omeprazole, esomeprazole, pantoprazole, rabeprazole, and lansoprazole. Omeprazole is also available over the counter (Losec®).

Clopidogrel can cause side effects on the gastrointestinal system and is therefore frequently prescribed together with a PPI.

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Which PPI?

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Long-acting beta-agonists in chronic obstructive pulmonary disease

United Kingdom — Chronic obstructive pulmonary disease (COPD) is a slowly progressive, mainly irreversible disease characterized by airflow limitation. It is one of the few diseases associated with an increasing mortality rate and, by 2020, is predicted to be the third most common cause of death.

The National Institute for Health and Clinical Excellence (NICE) and the Global initiative for chronic Obstructive Lung Disease (GOLD) guidelines recommend the addition of a long-acting beta-agonist (LABA) to short-acting beta-2 agonists when moderate COPD is diagnosed. The two LABAs currently licensed for treatment of COPD are salmeterol and formoterol (eformoterol). Both are licensed in COPD either as monotherapy or in conjunction with an ICS (fluticasone propionate and budesonide, respectively).

The Medicines and Healthcare Products Regulatory Agency (MHRA) has recently completed a comprehensive review of the use of LABAs, both as monotherapy and in combination with ICS. The review assessed published literature and unpublished trials investigating the efficacy or safety (or both) of LABA or LABA plus ICS against a range of clinical endpoints. The review concluded that:

- A LABA/ICS combination had greater efficacy than either LABA or ICS monotherapy in every study.

- The extent of the additional benefit provided by the LABA/ICS combination versus LABA alone was variable and was not always clinically significant. A convincing additional benefit of combination therapy was however seen in reduction in the rate of exacerbations.

- A significant additional benefit of the LABA/ICS combination has not been proven for milder disease and ICS should not be introduced earlier than guidelines suggest.

- In terms of efficacy, no clear dose-response relation was shown for either LABAs or ICS. To date, no treatment has been shown to influence the accelerated decline in lung function that is characteristic of COPD, highlighting the limited treatment options for this patient population.

A range of side effects have been reported after LABA or LABA/ICS therapy. However their incidence should be considered in the context of systemic inflammation and several co-existing conditions (including cardiovascular disease).

The overall benefits of long-acting beta-agonists (LABAs) both as monotherapy and in combination with inhaled corticosteroids (ICS) in the treatment of chronic obstructive pulmonary disease (COPD) continue to outweigh any risks. However, healthcare professionals are reminded that ICS should not be used alone in COPD. A key issue remains the increased risk of pneumonia associated with the use of ICS in COPD.

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Varenicline and bupropion: serious mental health events

United States of America — The Food and Drug Administration (FDA) has announced that it is requiring manufacturers to put a boxed warning on the prescribing information for the smoking cessation drugs varenicline (Chantix®) and bupropion (Zyban®). The warning will highlight the risk of serious mental health events including changes in behaviour, depressed mood, hostility, and suicidal thoughts when taking these drugs.

Similar information on mental health events will be required for bupropion marketed as the antidepressant Wellbutrin® and for generic versions of bupropion. These drugs already carry a boxed warning for suicidal behaviour in treating psychiatric disorders.

In addition, the FDA also is requesting more information in the Warnings section of the prescribing information and updated information in the Medication Guide for patients that further discuss the risk of mental health events when using these products.

Manufacturers will also be required to conduct a clinical trial to determine how often serious neuropsychiatric symptoms occur in patients using various smoking cessation therapies, including patients who currently have psychiatric disorders. The FDA's review of adverse events for patients using nicotine patches did not identify a clear link between those medications and suicidal events.

Reference: *Public Health Advisory*, 1 July 2009 at http://www.fda.gov

Pain medications containing propoxyphene: overdose

United States of America — The Food and Drug Administration (FDA) has taken action to reduce the risk of overdose in patients using pain medications such as Darvon® and Darvocet® that contain propoxyphene. Action was taken because of data linking propoxyphene and fatal overdoses.

The agency is requiring manufacturers of propoxyphene-containing products to strengthen the label, including the boxed warning, emphasizing the potential for overdose when using these products. Manufacturers will also be required to provide a medication guide to patients stressing the importance of using the drugs as directed.

In addition, the FDA is requiring a new safety study assessing unanswered questions about the effects of propoxyphene on the heart at higher than recommended doses. Findings from this study, as well as other data, could lead to additional regulatory action.

Propoxyphene has been on the market since 1957. It is widely prescribed and is used as a treatment for mild to moderate pain. The most frequent side effects of propoxyphene include lightheadedness, dizziness, sedation, nausea, and vomiting.

Reference: *FDA News Release*, 7 July 2009 at http://www.fda.gov

Latanoprost and rosiglitazone: macular edema

Australia — Macular edema causes blurred or distorted vision due to painless swelling of the macula. The condition is relatively common and is frequently associated with various ocular conditions including cataract surgery, age-related macular degeneration and, rarely, drug toxicity. Chronic macular edema or multiple recurrences may result in macular photoreceptor damage with permanent impairment of central vision (1).

To date, the Therapeutic Goods Administration (TGA) has received 25 adverse reaction reports of drug-associated macular edema. Most have implicated latanoprost (7 reports from a total of 216 for this drug) or rosiglitazone (9 reports from a total of 344), and three each have reported use of an NSAID or a bisphosphonate.

Latanoprost is a prostaglandin F_2-alfa analogue used as eye drops for the treatment of open angle glaucoma or ocular hypertension either alone (Xalatan®) or in combination with the beta-blocker timolol (Xalacom®). It reduces intraocular pressure by decreasing resistance and thereby increasing uveoscleral outflow of aqueous humor. It has not been found to have significant systemic pharmacological effects.

Macular edema is identified in the latanoprost product information as a potential adverse effect, more commonly occurring in patients with aphakia or pseudophakia with anterior chamber lenses and/or torn posterior lens capsule, or in patients with known risk factors for macular edema such as diabetic retinopathy and retinal vein occlusion. An association between the hypoglycaemic agent rosiglitazone and macular edema is also known. There is evidence that withdrawal of rosiglitazone is followed by resolution of macular edema (2, 3).

Macular edema should be suspected with any loss of visual acuity not correctible by pinhole refraction, and requires prompt specialist evaluation for confirmation of diagnosis and further measures as appropriate.

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 28, Number 3, June 2009 at http://www.tga.gov.au/adr/aadrb/aadr0906.htm#a1

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Metformin, dehydration and lactic acidosis

Australia — Lactic acidosis is a rare but extremely serious metabolic complication of metformin usage. The association has featured in two issues of the *Australian Adverse Drug Reaction Bulletin* (1, 2) and the following boxed warning on this serious reaction appears in product information for metformin-containing products:

"Life threatening lactic acidosis can occur due to accumulation of metformin. The main risk factor is renal impairment; other risk factors include old age associated with reduced renal function and high doses of metformin (> 2g/day).

'Metformin is contraindicated in acute conditions with the potential to compromise renal function, such as dehydration. This highlights the importance of educating patients about how to manage their diabetes, including their medications, when they become acutely unwell."

Since 1985, the Therapeutic Goods Administration (TGA) has received 141 reports of lactic acidosis associated with metformin, 25 of which described a fatal outcome. Many of the reports describe a recent history of diarrhoea, vomiting or gastrointestinal infection prior to the development of acidosis.

Patients should be educated about managing their diabetes and medications, particularly metformin, in the context of acute illness. If a patient on metformin develops vomiting and/or diarrhoea, especially when coupled with poor oral intake, they should see their doctor and consideration should be given to temporarily ceasing metformin until a normal dietary intake can be tolerated. Consideration should also be given to temporarily withholding any concomitant diuretic therapy, as this will exacerbate acute renal impairment in a dehydrated patient.

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 28, Number 3, June 2009 at http://www.tga.gov.au/adr/aadrb/aadr0906.htm#a1

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Montelukast: suicidality and other psychiatric reactions

Canada — Montelukast sodium (Singulair®), a leukotriene-receptor antagonist, is indicated for the prophylaxis and chronic treatment of asthma in patients two years of age and older (1). It is also indicated for the relief of symptoms of seasonal allergic rhinitis in patients 15 years of age and older when other treatments are not effective or not tolerated. Montelukast has been marketed in Canada since 1997.

Between September 2007 and July 2008, updates were made to the Canadian product monograph to include depression, suicidality and anxiety (1, 2). In March 2008, the US Food and Drug Administration (FDA) stated that it was

investigating further the suspected association between montelukast and suicidality (3). Following the FDA communication, there was a sevenfold increase in the number of montelukast-related cases reported to the Adverse Event Reporting System database in the United States (4).

From the date of marketing to 31 January 2009, Health Canada has received 13 adverse reaction (AR) reports related to suicidality or self-injury suspected of being associated with the use of montelukast.

From the date of marketing to 31 January 2009, Health Canada has received 29 other AR reports relating to depression, hostility or psychosis suspected of being associated with the use of montelukast.

Extracted from Canadian Adverse Reactions Newsletter, volume 19, issue 3, july 2009 at http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v19n3-eng.php

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Duloxetine: serotonin syndrome

Australia — Duloxetine (Cymbalta®) is a serotonin and noradrenaline reuptake inhibitor recently approved for the treatment of major depressive disorder. It was included on the Australian reimbursement system in June 2008 and, to up May 2009, over 200 000 prescriptions have been dispensed. Over this same period, 108 reports of suspected adverse drug reactions with duloxetine have been received. The commonly reported reactions include dizziness (10 cases), suicidal ideation (10), tremor (8), agitation (8) and serotonin syndrome (7).

Serotonin syndrome is caused by the accumulation of serotonin in the central nervous system. It is characterized by a triad of autonomic dysfunction, cognitive-behavioural changes and neuromuscular dysfunction. In five of the seven cases of reported serotonin syndrome, there was no evidence of other risk factors normally associated with this condition, such as concomitant use of other serotonergic agents or excessive dosing.

A case report published recently describes a 70 year old female who developed serotonin syndrome within 48 hours of commencing the drug (1). Symptoms rapidly resolved when duloxetine was ceased and re-emerged when duloxetine was re-introduced.

Based on this early post-market information, it appears that serotonin syndrome can occur with duloxetine treatment alone, even at therapeutic doses, as well as in combination with other drugs known to cause this syndrome. The Cymbalta® product information has recently been updated to reflect this new information (2).

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 28, Number 4, August 2009 at http://www.tga.gov.au/adr/adrac-bulletin

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Is it leflunomide lung?

Australia — The Australian Adverse Reactions Committee (ADRAC) continues to receive reports of severe pulmonary disease, including interstitial lung disease (ILD) in association with leflunomide (Arava®, Arabloc®). In some cases, the association with leflunomide was not recognized early enough and resulted in a fatal outcome.

Reports of ILD with leflunomide alone or in combination with methotrexate (also unilaterally associated with ILD) were described in two previous *Adverse Drug Reactions Bulletins* (1, 2). In December 2006, 142 of the 699 reports with leflunomide described respiratory symptoms including 22 of ILD. In June 2009, the number of leflunomide reports had increased to 845, 196 of which describe respiratory symptoms including 39 of ILD. Of the 196 reports describing respiratory symptoms, 78% described concomitant use of methotrexate; 23 of the 39 ILD reports involved this combination.

Although clinically variable, manifestations of drug-induced pulmonary toxicity commonly include fever, cough (especially dry and non-productive), dyspnoea, pleurisy, chest pain, hypoxaemia and/or radiological evidence of pulmonary infiltrates (usually diffuse and/or alveolar).

New onset or worsening pulmonary symptoms with or without associated fever in those taking leflunomide with or without methotrexate may indicate development of leflunomide lung and should prompt further investigation.

If ILD develops, discontinuation of these therapies and implementation of a washout with cholestyramine (as recommended in the leflunomide Product Information) may be appropriate (3).

In addition to ILD, leflunomide and methotrexate are both associated with a number of other severe, potentially fatal adverse effects, including liver failure, Stevens-Johnson syndrome and agranulocytosis. It is expected that the risks for ILD and other severe toxicities would be at the least additive when these drugs are used concomitantly.

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 28, Number 4, August 2009 at http://www.tga.gov.au/adr/adrac-bulletin

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Isotretinoin and acquired hearing impairment

Australia — Isotretinoin is a retinoid therapy indicated for the treatment of severe cystic acne unresponsive to conventional treatments.

Isotretinoin therapy has been associated with acquired hearing impairment in previously well individuals, although the mechanism/s have not been established. This should not be confused with congenital hearing impairment, which is a known potential complication following fetal exposure to isotretinoin in-utero.

The Therapeutic Goods Administration (TGA) has received 609 adverse event reports for isotretinoin dating back to 1982. These include two cases of unilateral hearing loss, one case of hearing loss at low frequencies and two cases of tinnitus. Isotretinoin was the sole suspect in all five cases. The ages ranged from 14

to 46 years of age and, where reported, duration of therapy ranged from 2–8 months. In all cases the outcomes were unknown.

Prescribers are reminded that isotretinoin has been associated with acquired hearing impairment which can be unilateral or bilateral. Symptoms may include tinnitus, impaired hearing at certain frequencies and deafness. It is unknown whether hearing impairment is permanent. If isotretinoin-associated auditory toxicity is suspected, the drug should be ceased and the patient referred for audiology assessment.

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 28, Number 4, August 2009 at http://www.tga.gov.au/adr/adrac-bulletin

Pharmacovigilance Focus

Safety of medicinal products

The World Health Organization's (WHO) Advisory Committee on Safety of Medicinal Products (ACSoMP) meets regularly to provide advice on current pharmacovigilance policy and issues related to the safety and effectiveness of medicinal products. The following summary captures much of the discussion and recommendations from the Committee's Sixth Meeting in 2009.

Global awareness of medicines safety
A CD-ROM is being prepared for those interested in pharmacovigilance. A key objective is to highlight the importance of risk-benefit assessment based on information available. It is hoped that the CD-ROM will further convince governments of the cost-effectiveness of implementing a pharmacovigilance system.

Three phases are proposed as a framework for action.

- social marketing.
- identifying a medium for disseminating messages.
- creating social networking through patient participation.

Developing impact indicators specific to pharmacovigilance
Discussion on benchmarking and outcome assessment in pharmacovigilance covered rationale for pharmacovigilance indicators, broad and specific objectives, characteristics, types of indicators, data sources and the process of developing indicators. Structural indicators, process indicators and outcome (impact) indicators were also reviewed and ACSoMP agreed that both core and supplementary indicators should be developed.

A sub-group was assigned to continue developing a set of practical indicators for developing countries. These will be prepared in draft for presentation at the annual meeting of National Pharmacovigilance Centres to be held in Morocco in November 2009 and a final draft will be resubmitted to the next meeting of ACSoMP in 2010.

Guidelines for acute safety issues management
This item dealt with the management of acute safety issues by regulatory authorities. Major considerations focused on:

- evidence for decision-making after signal detection.
- analytical and methodological challenges.
- optimal design and organization of a signal detection system.
- signal detection and public health.
- risk communication.

Several matters were discussed including how people in developing countries react when regulatory decisions are made in developed countries which impact on their work. Also what should constitute the basis for decisions and how to prepare for any potentially embarrassing public health crisis.

Two associated issues were also considered. The first was how and when to take action on an acute drug safety issue and the second was how to communicate and

share information once action has been taken so that others can appreciate the underlying reasons. The need for development of a protocol was identified to help in dealing with acute safety issues in light of limitations in the WHO ICSR (Individual Case Safety Reports) database in providing complete information. While WHO should provide leadership and guidance, national governments and regional agencies need to take on local roles and responsibilities. Confidentiality agreements regarding information exchange should be made by and among all members of the WHO International Drug Monitoring Programme rather than bilaterally or within specific regions.

Members agreed that ACSoMP should design a protocol on how and when to take action on drug safety issues. However, when it comes to information sharing between regulators, the appropriate platform would be the International Conference for Drug Regulatory Authorities (ICDRA). Consequently, a recommendation will be made to the planning committee for the 14th ICDRA to include a session on information sharing between regulators. A guideline for the management of acute safety issues will be prepared accordingly.

International network of safe medication practice centres

The International Medication Safety Network (IMSN) is a growing network of countries that are working together to promote safe medication practices. The IMSN Group made a presentation on why pharmacovigilance centres should be concerned with medication error reports. Medication errors are a system issue and involve different regulatory bodies. Since there may be reluctance to report medication errors for fear of litigation and punitive measures, there is a need to develop strategies to encourage reporting.

It was recommended that a training workshop and/or group activity should be organized in parallel with the next annual meeting of National Pharmacovigilance Centres to share common concerns and objectives, and to facilitate collaboration between IMSN and pharmacovigilance networks.

Collaboration with the Expert Committee on the Selection and Use of Essential Medicines

A comprehensive draft guideline on the safety evaluation of medicines was presented, outlining the information needed to accompany an application for inclusion or deletion of a medicine in the WHO Model List of Essential Medicines (EML).

General issues concerning safety evaluation requirements were discussed including sources of information, advice on the handling of safety information, drug administration, adverse drug reactions and references. Consideration was given to whether every new EML application should be accompanied by a risk management plan for the medicine involved. In which case, risk management plans should cover any adverse drug reaction already known to be associated with use of a medicine. It was also suggested that cohort event monitoring studies should accompany the deployment of any new medicine being proposed for mass administration in order to ensure that potential problems are quickly identified before patients are affected.

Current EML applications do not contain sufficient information to provide an adequate safety evaluation. The safety component of most applications passed to ACSoMP for assessment until now meet neither the proposed guidelines nor the current requirements. Consequently, there is a need for applicable guidelines.

ACSoMP is willing to provide guidance and leadership in the development and

adoption of these guidelines. The principles of the new guideline on safety evaluation of products proposed for inclusion in the EML should be complete, up-to-date, rigorous, and scientifically valid. These principles should be applicable to all safety assessments for the EML. This proposal will be presented to the next meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines.

Public access to signals
A proposal was made to open the WHO ICSR database to the public and provide wider distribution of the signal document. In principle, opening the WHO database to the public and consumers was supported. However, it was agreed that the narrative section should remain hidden in order to protect patient confidentiality. It was also noted that publication in the scientific media was a way of promoting pharmacovigilance activities spearheaded by WHO and the Uppsala Monitoring Centre (UMC).

The Committee therefore agreed that it would be acceptable to provide information without narrative to academia to help with research provided there is a declaration of interest and the usual caveats inserted. The proposal will be revised accordingly and presented at the next annual meeting of National Pharmacovigilance Centres and the subject of making the signal document more available will be discussed further.

Global strategy for best practice in pharmacovigilance
The broad outline of a global strategy for best practice in pharmacovigilance was presented. It is part of the overall WHO strategy for the next five years, with which the UMC four-year plan will be aligned. The principal objectives will be to provide an advocacy tool for stakeholders, to develop a plan for a health systems approach to pharmacovigilance and to build cost-effective pharmacovigilance systems with a broad scope to respond to questions covering several health areas. ACSoMP was requested to discuss specific strategic components and help identify a core group to lead the development. Consequently, a document will be drafted for circulation and comment by other ACSoMP members and presented at the annual meeting of National Pharmacovigilance Centres.

Leishmaniasis
Safety monitoring of medicines used in the leishmaniasis elimination programme in Bangladesh, India and Nepal was described. The presentation included an assessment of the risk of preventable ADRs using surrogate markers, risk minimization through use of checklists of precautions and contra-indications, use of patient cards, training and supervision of healthcare workers, analysis of ADRs, and evaluation of pharmacovigilance activity. There are serious safety concerns concerning miltefosine, a recently developed medicine which is effective in controlling the disease. In this respect, control programmes should work closely with pharmacovigilance personnel to develop risk management and risk minimization plans.

Chagas disease
WHO activities in the area of Chagas disease were presented. In 2007, WHO and Bayer Healthcare agreed on distributing 500 000 tablets of nifurtimox free of charge each year. Chagas disease, which used to be encountered only in Latin America, is now present in other regions of the world including Europe and the Western Pacific. In 2008, for example, around 150 patients were diagnosed in Geneva, Switzerland, with Chagas disease within a period of six months.

Currently, there are two medicines available for Chagas disease: nifurtimox and benznidazole, both developed in the 1960s. In Bolivia, deaths have been

reported in children following incorrect use of nifurtimox. WHO is assisting with the distribution of benznidazole and nifurtimox, both of which are on the WHO Essential Medicines List.

Even though nifurtimox and benznidazole were developed in the 1960s, available information on safety is limited. It is important not only to implement pharmacovigilance but also to consider what kind of operational research needs to be implemented to ensure the collection, analysis and dissemination of safety information on these products to patients and healthcare providers. Further discussion is necessary to determine optimal pharmacovigilance systems in these settings.

Vaccines
A dedicated vaccine safety specialist has been appointed at the WHO Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre) to strengthen the signal detection process and improve tools used for reporting vaccines. Activities are being undertaken to address key safety challenges with new vaccines, such as quality of safety data in individual countries, capacity to respond to crises, quality of data for signal detection and risk assessment at global level. Activities also include routine capacity strengthening, developing a global crisis management plan and strengthening the Global Network for Postmarketing Surveillance of Newly Prequalified Vaccines. The Network will provide data and support to the WHO vaccine prequalification system by generating data in the postmarketing phase.

Other collaboration between the WHO vaccines and medicines safety departments and the UMC includes development of a vaccine dictionary (part of the WHO Drug Dictionary) and an ATC classification for vaccines. The Global Advisory Committee on Vaccine Safety (GACVS) continues to provide support and oversight on all activities related to vaccine safety and acts as an independent advisory committee to WHO. A member of ACSoMP serves on GACVS to ensure collaboration and sharing of information.

Malaria
A presentation was made on the rationale and need for collaboration between malaria and medicines safety programmes in WHO, challenges at country, regional and global levels, and the way forward to improving access to artemisinin combination therapy (ACT). The move to deregulate ACT to over the counter medicines as a way to improve treatment will involve home-based care. The way forward will be to promote risk management plans, empower consumers, and strengthen integration between pharmacovigilance and public health programmes.

The Affordable Medicines Facility for Malaria (AMFm) aims to lower the net cost of ACTs and expand availability for this treatment. The initiative should be accompanied by increased safety monitoring for these medicines in all settings and under all conditions of use. The first phase of the AMFm will be rolled out in eleven countries and will provide a challenge and an opportunity to develop pharmacovigilance systems and strengthen those already existing.

Various initiatives run by different organizations exist in the area of pharmacovigilance of antimalarials and tropical diseases in general. These activities should be coordinated and members suggested that WHO should take a leading role in coordinating these initiatives which involve several different players. ACSoMP should be informed of all the safety studies being undertaken so that it can provide independent scientific and technical advice to WHO and Member States. Future WHO plans in this disease area include a meeting with the Medi-

cines for Malaria Venture (MMV) and other partners to develop a joint protocol and guidelines for the pharmacovigilance of antimalarials. Such joint meetings will ensure harmonization in safety monitoring. An ACSOMP member will assist WHO by coordinating various ongoing initiatives in Africa.

HIV/AIDS
A presentation was made on methods to improve the safety of antiretroviral medicines (ARVs) in public health use, pharmacovigilance for ARVs — including identifying gaps and needs — and a pilot project for improving the safety of ARVs.

Different toxicities are expected of medicines when used for post-exposure prophylaxis of HIV and management of patients with HIV/AIDS. As more and more people stay on treatment, toxicities are becoming an important issue. Gap analysis has identified specific needs in ART programmes such as development of additional definitions and newer methodologies for capturing data relating to toxicity. Towards this, a pilot project that is being funded by the Bill and Melinda Gates Foundation will establish internationally agreed reporting tools, strengthen pharmacovigilance capacity in selected countries, support key studies, and coordinate the analysis of safety data on ARVs.

Switching of patients from a first to second-line regimen has huge cost implications. Safety data on ARVs is very limited regarding a second-line regimen. For example, the pharmacokinetic effects of protease inhibitors in children are little documented. It is particularly important to learn the reasons why patients are switched. Subjective reasons may dominate the switching of patients and this must be determined.

ACSoMP agreed that guidelines on management of adverse events and treatment limiting toxicities should be developed and disseminated to all countries. Given the issues of co-morbidity and drug interactions, collaboration with other programmes is important to ensure the safe use of ARVs.

Review of artesunate+amodiaquine
Based on a draft proposal for action, the safety issues of artesunate+amodiaquine (ASAQ) were discussed. A meeting with DNDi and Sanofi-Aventis had resulted in a risk management plan for ASAQ. Sanofi-Aventis is currently carrying out studies in Cote d'Ivoire on the real-life safety of this fixed dose combination. Weaknesses in the study design were identified and discussed by ACSoMP. Several groups are planning to undertake active ASAQ pharmacovigilance but there are currently delays in engaging key personnel and local associations. Safety and use of concomitant medicines administered with ASAQ should also be studied.

ACSoMP members will review the risk management plans and offer suggestions to WHO. In addition, a consultant, currently reviewing some adverse events reported with ASAQ will be requested to outline the safety profile of ASAQ.

Pharmacovigilance and dependence inducing drugs
Feedback on use of pharmacovigilance data for the assessment of dependence and abuse potential of drugs of dependence has been generated through e-mail consultation. Conclusions point out that pharmacovigilance is useful for evaluating drug dependence liability but that a distinction should be made between ADRs from clinical trials and those made from spontaneous reporting. It was agreed that using defined daily doses (DDDs) provided the best assessment tool. Various drug classes should continue to be dealt with separately.

A presentation on "opioids, safety surveillance and risk management: elaborating key challenges in the review of postmarketing safety information on opioids in the USA" was made. Quantifying known

adverse events including those which indicate abuse is very difficult. While geographic clustering of abuse and abuse potential may occur, reporting practices are variable and many reports focus on the active ingredient rather than the finished product.

Understanding prescribing decisions is very hard in post-approval setting. The number of persons at risk is often unknown and information is not always available in a timely manner. There are also several important factors that are difficult to ascertain in spontaneous reports, including medication theft, overuse of prescribed medication, abuse/dependence/addiction, overdose, nonprescription use, etc. It is also important to understand the abuse potential of new formulations. Thus, definitions related to abuse potential should be broadened to include non-opioids. The legal classification for products is also an important issue which needs attention.

Ethics in observational studies
A wider understanding of the importance of ethical aspects of epidemiological and observational studies must be recognized globally. There are currently few documents discussing ethical review and ethical applications in pharmacovigilance. The Council for International Organizations of Medical Sciences (CIOMS) has recently published *International Guidelines for Ethical Review of Epidemiological Studies*.

Ethical committee approval must be sought in all settings and in particular where there are vulnerable groups and populations. In preparing a study protocol, it is important to comply with national legislation and internationally approved guidelines in order to ensure that studies are scientifically and ethically acceptable.

Internet connectivity in Africa
A WHO initiative Africa Health Infoway has been launched to improve internet connectivity in Africa. Expected deliverables include better access to information, telemedicine, e-Learning, and disease surveillance. Since WHO's mandate does not include establishing internet infrastructure, a collaborative agreement has been entered into with the International Telecommunications Union. Partnerships have also been set up with regional organizations, including the African Union Commission through which funding is being sought.

Several initiatives are aimed at improving Internet infrastructure in Africa. One initiative, the Telemedicine Task Force, involves the European Space Agency, the European Union, African Union, WHO and others. This initiative proposes the use of satellite technology for e-health. ACSoMP has requested updates on progress and has proposed collaborating by communicating the usefulness of this project to management, policy makers, and donors.

The WHO Medicines Safety team has proposed cooperation with Africa Health Infoway in the following ways.

• The pharmacovigilance programme tools VigiFlow and CEMFlow will be incorporated into the AHI plan.

• A priority list of countries will be identified for support by this initiative.

• Promotion of Africa Health Infoway will be made in all workshops.

Review of existing definitions
Support is strong for a review of existing definitions in pharmacovigilance. This topic was also discussed at the annual meeting of National Pharmacovigilance Centres in 2008. Signals and adverse reactions/adverse events are top priorities. During the past year, the CIOMS Working Group on Signal Detections has been moving ahead with new definitions.

ACSoMP was requested to provide guidance on WHO's role in this activity.

ACSoMP agreed that WHO should take this activity forward because it has the mandate and capacity to coordinate activities for developing global norms and standards. Led by ACSoMP, the WHO Programme for International Drug Monitoring should prepare a set of definitions. A concept paper will be drafted for the next annual meeting of National Pharmacoviiglance Centres.

Reference: *WHO Pharmaceuticals Newsletter* No. 3, 2009 at http://www.who.int/medicines

Regulatory Action and News

Withdrawal of dextropropoxyphene

European Union — Finalizing a review of the safety and efficacy of dextropropoxyphene-containing medicines, the European Medicines Agency (EMEA) Committee for Medicinal Products for Human Use (CHMP) concluded that the risks, particularly the risk of potentially fatal overdose, are greater than the benefits. The Committee therefore recommended that the marketing authorizations for these medicines be withdrawn across the European Union. The withdrawal will be gradual to allow time for the safe transfer of patients to appropriate alternative therapies, in line with national recommendations.

Dextropropoxyphene is a painkiller used to treat acute and chronic pain. It has been available as a prescription-only medicine for about 40 years, either on its own or in combination primarily with paracetamol, as tablets, capsules, suppositories and solutions for injection.

The Agency's recommendation has been forwarded to the European Commission for the adoption of a legally binding decision.

Reference: *Press Release*, Doc. Ref. EMEA/401062/2009. 25 June 2009 at http://www.emea.europa.eu/pdfs/human/opinion

Besifloxacin: approved for bacterial conjunctivitis

United States of America — The Food and Drug Administration (FDA) has approved besifloxacin ophthalmic suspension 0.6 percent (Besivance®) for the treatment of bacterial conjunctivitis (non-viral).

Bacterial forms of conjunctivitis are common in childhood but can occur in people of any age. Symptoms of bacterial conjunctivitis include red eyes, swelling, eyelids sticking together, itching, watering and a white or yellow sticky discharge from the eyes. Bacterial conjunctivitis is generally a condition that runs its course in 7–14 days.

Patients using the drug in clinical trials had a faster rate of resolution of infection than those treated with a solution containing only a preservative. The drug was shown to be effective in treating patients age one year and older.

Adverse events were reported in less than three percent of patients in clinical trials. Adverse reactions included redness of the eyes, blurred vision, eye pain, irritation and itching, and headache.

Reference: *FDA News Release*, 6 July 2009 at http://www.fda.gov

Prasugrel: approved for angioplasty patients

United States of America — The Food and Drug Administration (FDA) has approved the blood-thinning drug prasugrel (Effient® tablets) to reduce risk of blood clots forming in patients who undergo angioplasty.

During an angioplasty, a balloon is used to open the artery that has been narrowed by atherosclerotic plaque.Often, a stent is inserted into the blood vessel to help keep the artery open after the procedure. Platelets in the blood can clump around the procedure site, causing clots that may lead to heart attack, stroke, and death.

The fraction of patients who had subsequent non-fatal heart attacks was reduced from 9.1% in patients who received Plavix® to 7.0% in patients who received Effient®. While the numbers of deaths and strokes were similar with both drugs, patients with a history of stroke were more likely to have another stroke while taking Effient®. In addition, there was a greater risk of significant, sometimes fatal bleeding seen in patients who took Effient®.

The drug's labeling will include a boxed warning alerting physicians that the drug can cause significant, sometimes fatal, bleeding.

Reference: *FDA News Release*, 10 July 2009 at http://www.fda.gov

Pemetrexed: approved for advanced lung cancer

United States of America — The Food and Drug Administration (FDA) has approved pemetrexed (Alimta®), the first drug available for maintenance therapy of advanced or metastatic lung cancer.

Pemetrexed disrupts metabolic processes that are dependent on the B-vitamin folate, a necessary ingredient for cell replication. Non-small cell lung cancer has several subtypes, including squamous cell, large cell, adenocarcinoma and mixed histology cancers. In a 600-patient clinical trial, people with predominantly squamous cell cancer did not benefit from Alimta® but those with other subtypes of non-small lung cancer survived an average 15.5 months following treatment compared with 10.3 months for patients who received an inactive substance (placebo). All patients in the study received standard medical care.

Reported adverse events included damage to blood cells, fatigue, nausea, loss of appetite, tingling or numbness in the hands and feet, and skin rash.

Alimta® was initially approved in 2004 for the treatment of patients with mesothelioma, a cancer frequently related to asbestos exposure. The drug was later approved for the treatment of patients with non-small cell lung cancer whose disease worsened on prior chemotherapy drugs and also as an initial therapy for advanced non-small cell lung cancer.

Reference: *FDA News Release*, 2 July 2009 at http://www.fda.gov

Dronedarone: approved for heart rhythm disorder

United States of America — The Food and Drug Administration (FDA) has approved dronedarone (Multaq®) to help maintain normal heart rhythm in patients with a history of atrial fibrillation or atrial flutter. The drug is approved for use in patients whose hearts have returned to normal rhythm or will undergo drug or electric-shock treatment to restore a normal heart beat.

Multaq® may cause critical adverse reactions, including death, in patients with recent severe heart failure. The drug's label will contain a boxed warning cautioning that the drug should not be used in severe heart failure patients.

In a multinational clinical trial with more than 4600 patients, Multaq® reduced cardiovascular hospitalization or death from any cause by 24%, when compared with placebo. Most of that effect represents reduced hospitalizations, especially those related to atrial fibrillation.

The most common adverse reactions reported by patients in clinical trials were diarrhoea, nausea, vomiting, fatigue and weakness.

Reference: *FDA News Release*, 2 July 2009 at http://www.fda.gov

First advanced therapy medicinal product approved

European Union — The European Medicines Agency (EMEA) has recommended the first marketing authorization for an advanced therapy medicinal product following a positive opinion from the Agency's Committee for Advanced Therapies (CAT) and the Committee for Medicinal Products for Human Use (CHMP). The CAT, is a multidisciplinary committee that brings together experts in gene therapy, somatic cell therapy and tissue engineering.

ChondroCelect® is a cell-based medicine that is used to repair defects in the cartilage of the femoral condyle (the end of the thighbone) in the knee. It consists of chondrocytes (cartilage-forming cells) that are taken from a healthy region of the patient's cartilage, grown outside the body, and then re-implanted during surgery.

This is the first product to benefit from the new legal and regulatory framework for advanced therapy medicinal products (Regulation (EC) No. 1394/2007). This framework is designed to ensure the free movement of advanced medicines within the European Union (EU), to facilitate their access to the EU market, and to foster the competitiveness of European pharmaceutical companies in the field while guaranteeing the highest level of health protection for patients.

Reference: *Press Release*, Doc. Ref. EMEA/CHMP/394741/2009. 26 June 2009 at http://www.emea.europa.eu/pdfs/human/opinion

Gemifloxacin: withdrawal of marketing authorization application

European Union — The European Medicines Agency (EMEA) has been formally notified of the decision to withdraw an application for a centralized marketing authorization for the medicine Factive® (gemifloxacin), 320 mg film-coated tablets. Factive® was expected to be used for the treatment of bacterial infections causing mild to moderate community-acquired pneumonia and acute exacerbation of chronic bronchitis.

At the time of the withdrawal, it was under review by the Agency's Committee for Medicinal Products for Human Use (CHMP). In its official letter, the company stated that the withdrawal of the application was based on the CHMP's view that the data provided did not allow the Committee to conclude on a positive benefit-risk balance.

Reference: *Press Release*, Doc. Ref. EMEA/382408/2009. 23 June 2009 at http://www.emea.europa.eu/

Saxagliptin approved for diabetes

United States of America — The Food and Drug Administration (FDA) has approved saxagliptin (Onglyza®), a once-daily tablet to treat Type 2 diabetes in adults. The medication is intended to be used with diet and exercise to control high blood sugar levels. Saxagliptin is in a class of drugs known as dipeptidyl peptidase-4 (DPP-4) inhibitors which stimulate the pancreas to make more insulin after eating a meal.

The most common side effects observed with saxagliptin are upper respiratory tract infection, urinary tract infection, and headache. Other side effects include allergic-like reactions such as rash and hives.

Approval of Onglyza® was primarily based on the results of eight clinical trials. The application seeking FDA approval was submitted before December 2008 when the agency recommended that manufacturers of new diabetes drugs

carefully design and evaluate their clinical trials for cardiovascular safety. Although saxagliptin was not associated with an increased risk for cardiovascular events in patients who were mainly at low risk for these events, the FDA is requiring a postmarket study that will specifically evaluate cardiovascular safety in a higher risk population.

Reference: *FDA News Release*, 31 July 2009 at http://fda.hhs.gov

Contusugene ladenovec: withdrawal of application for marketing

European Union — The European Medicines Agency (EMEA) has been formally notified by the manufacturer of the decision to withdraw its application for a centralized marketing authorization for the medicine contusugene ladenovec (Contususgene ladenovec Gendux®) suspension for injection expected to be used for the treatment of squamous cell carcinoma in head and neck cancer.

In its official letter, the company stated that the withdrawal of the application was based on the difficult financial situation of its parent company which prohibits them to fund further activities related to this application.

***Reference**: Press Release*, Doc. Ref. EMEA/412751/2009. 23 July 2009 at http://www.emea.europa.eu

Rotigotine transdermal patch: restrictions lifted

European Union — The European Medicines Agency has recommended that the supply and treatment restrictions for rotigotine transdermal patch (Neupro®), be lifted. Once this recommendation is endorsed by the European Commission, the ban on prescribing Neupro® to patients not yet taking the medicine will be reversed. Doctors in the European Union will then be able to prescribe Neupro® to all patients in accordance with the approved product information. Prescriptions will no longer be limited to one month.

Rotigotine transdermal patch is currently indicated for the treatment of Parkinson disease and restless legs syndrome. It is applied as transdermal patches that deliver the active substance, rotigotine, across the skin.

At its May 2008 meeting, the Agency's Committee for Medicinal Products for Human Use (CHMP) recommended immediate changes to the storage conditions for Neupro following reports of crystallisation of the active substance in some patches. The recommendations included the requirement that the medicine be stored in a refrigerator at a temperature of between 2 and 8 °C.

Following assessment of the cold-chain system that has been put in place by the company, the CHMP is now re-assured that no significant crystallisation should occur under these storage conditions and that Neupro® supplied to patients now meets the required quality standards.

Reference: *Press Release*, Doc. Ref. EMEA/CHMP/322964/2009. 29 May 2009

Impact of European Clinical Trials Directive

The Impact on Clinical Research of European Legislation Project (ICREL) was a one-year project financed by the European 7th Framework Programme and coordinated by the European Forum for Good Clinical Practice (EFGCP). The European Clinical research Infrastructures Network (ECRIN), the European Organization for research and Treatment of Cancer (EORTC), as well as the Hospital Clínic of Barcelona and the Ethics Committee of the Medical University of Vienna collaborated in this project.

Its aim was to measure and analyse the direct and indirect impact of the Clinical Trials Directive 2001/20/EC and related legislations in the EU on all categories of clinical research and on the different stakeholders: commercial and non-commercial sponsors, ethics committees and competent authorities. This initiative responds to the need to adapt the current legislation and will help determine the most relevant pathways for improvement.

Directive 2001/20/EC was adopted with the objective of harmonizing the EU regulatory environment for clinical research, improving the protection of participants, optimizing the use of safety information, and ensuring the credibility of data through strengthened responsibility of the sponsors and harmonized trial authorization procedures for Member States.

However, this legislation only protects participants in clinical trials on medicinal products. It requires almost similar procedures for all types of clinical trials with medicinal products from registration studies on innovative treatments to studies comparing treatment strategies using marketed drugs or applying minimally invasive procedures. Academic institutions and industry, including SMEs, face major difficulties in fulfilling sponsor responsibilities.

The Clinical Trials Directive objectives were transposed into divergent national legislations, partly missing the harmonization goal and making multinational trials, in particular, difficult to perform. This could raise doubts about the competitiveness and attractiveness of the EU for clinical research. The ICREL project was designed to measure the impact of the current EU legislation, analysing its direct and indirect consequences.

In order to reach a maximum of information, a survey was conducted. The first results of this survey were presented and discussed during a conference in Brussels in December 2008. Conclusions of the meeting are presented in a final report which has been published by the European Commission.

Reference: European Forum for Good Clinical Practice (EFGCP) at http://www.efgcp.be/ICREL/

WHO list of recently prequalified medicinal products

The following products have recently been added to the list of prequalified products by the WHO Prequalification of Medicines Programme. (http://www.who.int/prequal). This additional list covers the period 1 January 2009 to 2 July 2009.

Product	Presentation	Manufacturer
Abacavir(as sulfate) +Lamivudine+Zidovudine	Tablets 60mg +30mg+60mg	Matrix Laboratories Sinnar, Maharashtra,India
Ciprofloxacin	Infusion 2mg/ml	Claris Life Sciences Ahmedabad, Gujarat, India
Efavirenz	Tablets 200mg	Strides Arcolab, Bangalore, India
Efavirenz	Tablets 600mg	Strides Arcolab, Bangalore, India
Efavirenz	Tablets 600mg	Hetero Drugs, Hyderabad, India

Continued ...

WHO list of recently prequalified medicinal products *(Continued)*

Product	Presentation	Manufacturer
Lamivudine +Nevirapine+Zidovudine	Film-coated tablets 150mg+200mg+300mg	Cipla Goa, India
Lamivudine +Nevirapine+Zidovudine	Tablets 150mg +200mg+300mg	Matrix Laboratories Sinnar, Maharashtra, India
Lamivudine +Stavudine	Tablets 150mg+30mg	Aurobindo Pharma Hyderabad, India
Lamivudine +Stavudine	Tablets 150mg+40mg	Aurobindo Pharma Hyderabad, India
Lopinavir +Ritonavir	Tablets 200mg+50mg	Matrix Laboratories Sinnar, Maharashtra, India
Lopinavir +Ritonavir	Tablets 100mg+25mg	Matrix Laboratories Sinnar, Maharashtra, India
Lamivudine +Zidovudine	Tablets 30mg+60mg	Matrix Laboratories Andhra Pradesh, India
Nevirapine	Oral susp. 50mg/5ml	Cipla, Unit-1, Goa India
Tenofovir disoproxil fumarate	Tablets 300mg	Cipla, Goa, India
Oseltamivir (as phosphate)	Capsules 75mg	Cipla, Goa, India
Artemether +Lumefantrine	Tablets 20mg+120mg	Cipla, Patalganga, India
Artemether +Lumefantrine	Dispersible Tablets 20mg+120mg	Novartis Pharma Suffern, USA
Ethinylestradiol +Levonorgestrel	Tablets 30µg+150µg	Bayer Schering Pharma Weimar, Germany
Levonorgestrel	Tablets 30µg	Bayer Schering, Weimar, Germany
Cycloserine	Capsules 250mg	Aspen Pharmacare Port Elizabeth, South Africa
Isoniazid +Pyrazinamide+Rifampicin	Tablets 30mg+150mg+60mg	Macleods Pharmaceuticals Kachigam, Daman, India
Rifampicin +Isoniazid	Tablets 60mg+30mg	Macleods Pharmaceuticals Kachigam, Daman, India
Pyrazinamide	Tablets 400mg	Micro Labs, Hosur, Tamilnadu, India
Pyrazinamide	Tablets 500mg	Micro Labs, Hosur, Tamilnadu, India

Current Topics

Forum on international pharmaceutical crime

The Permanent Forum on International Pharmaceutical Crime (PFIPC) comprises members from 15 countries throughout the world: Australia, Belgium, Canada, Germany, Ireland, Israel, Italy, Netherlands, New Zealand, Singapore, South Africa, Spain, Switzerland, United Kingdom and United States of America. Members come from both pharmaceutical regulatory and law enforcement components of member countries with the objective of combating worldwide pharmaceutical crime.

International Conference on Pharmaceutical Crime
The Swiss Agency for Therapeutic Products, Swissmedic, as a member of PFIPC and the International Laboratory Forum on Counterfeit Medicines (ILFCM) has organized the annual conference for these two organizations in Bern from 8–12 June 2009.

A total of 33 delegates from 18 countries attended the conference. Participants included enforcement experts and representatives from international organizations that work to fight against pharmaceutical crime. The conference enabled delegates to exchange experience and information about trends and activities and develop joint projects to improve international collaboration. Particular emphasis was placed on preparing coordinated action against illegal Internet trade in therapeutic products.

The PFIPC also supports the work of the International Medical Products Anti-Counterfeiting Taskforce (IMPACT), an initiative of the World Health Organization (www.who.int/impact/en/). IMPACT is aimed at combating counterfeit medicines in countries with a high proportion of counterfeit products but with insufficient enforcement facilities of their own. Many experts from the PFIPC work in international organizations and promote global collaboration.

Experts from ILFCM international control laboratories in 10 countries met in parallel to this conference to exchange experiences. The meeting featured presentations on new technological developments in the analysis of counterfeit pharmaceuticals and focused on tracking new illegal products. These medicines, which are mainly sold over the Internet without any correct indication of ingredients often contain new active substances of largely unknown effect and which may be hazardous when ingested by humans.

Discussions in both conferences showed once again that repeated published warnings about purchasing pharmaceuticals from illegal sources, especially over the Internet, are justified. International pharmaceutical crime is on the increase and illegally sold medicines are a major risk to the health of the general public.

Reference: http://www.swissmedic.ch/aktuell/

Illegal online medicine suppliers targeted

The first international Internet day of action co-coordinated by the Permanent Forum on International Pharmaceutical Crime (PFIPC), INTERPOL and the International Medical Products Anti-Counterfeiting Taskforce (IMPACT), has targeted illegal online sale of medicines to

the public. This action has resulted in a series of arrests and the seizure of potentially harmful medicines in operations carried out around the world. Codenamed Pangea, the operation focused on those individuals behind Internet sites which illegally sell and supply unlicensed or prescription-only medicines claiming to treat a range of ailments.

While many countries have previously carried out individual law enforcement activities targeting 'Internet pharmacies', Operation Pangea was the first time that action was taken on an international scale, with participating countries. (Australia, Canada, Germany, Ireland, Israel, New Zealand, Singapore, Switzerland, United Kingdom and United States of America.)

Locations in each country were identified, with investigators visiting residential and commercial addresses relating to Internet sites believed to be selling unlicensed or prescription-only medicines claiming to treat many conditions such as diabetes, obesity or hair loss.

Investigations in a number of countries are still ongoing, with the final results from Operation Pangea to be released upon their conclusion. For more information on individual activities and operations, please contact the national enforcement agencies in the countries concerned.

Reference: Illegal online medicine suppliers targeted in first international Internet day of action. *Interpol media release.* http://www.interpol.int

Elimination of river blindness in Mali and Senegal

The first evidence that onchocerciasis elimination is feasible with ivermectin treatment has been published in the open-access journal *PLoS Neglected Tropical Diseases*. Onchocerciasis often blinds people, as well as causing debilitating skin disease. Over 37 million people are infected, often living in poor, rural African communities. The multi-country study showed that treatment with ivermectin stopped further infections and transmission in three specific endemic areas in Africa.

Ivermectin kills the larvae but not the adult worms of *Onchocerca volvulus*, the parasite that causes the disease, so annual or biannual treatments are required to prevent resurgence. Donations of the drug by the manufacturer to countries where onchocerciasis is endemic have resulted in annual treatments to all eligible community members — over 60 million people in 26 African countries in 2008.

This new study in three areas in Mali and Senegal where onchocerciasis was endemic has provided the first evidence of the feasibility of onchocerciasis elimination with ivermectin in endemic areas in Africa. The studies showed that after 15 to 17 years of six-monthly or annual treatments, only a few infections remained in the human population and transmission levels were below predicted thresholds for elimination.

References:

1. News on UNICEF/UNDP/WorldBank/WHO-TDR http://www.who.int/tdr/svc/news-events

2. Full article available at http://www.plosntds.org/article/info%3Adoi%2F10.1371%2Fjournal.pntd.0000 497

3. TDR press release, 21 July 2009 http://www.who.int/tdr/svc/news-events/news/onchocerciasis-elimination

Moxidectin for river blindness in phase III clinical trials

A clinical trial is being launched in three African countries of a medicine that could

speed up elimination of onchocerciasis, one of the leading infectious causes of blindness across Africa. The medicine, moxidectin, is being investigated for its potential to kill or sterilize the adult worms of *Onchocer-ca volvulus* which cause onchocerciasis.

Onchocerciasis, also called river blindness, is transmitted by the blackfly which breeds in fast flowing rivers. Blindness is the most incapacitating symptom of the disease which also causes debilitating skin disease.

The development of moxidectin for onchocerciasis is being conducted through a collaboration of the Special Programme for Research and Training in Tropical Diseases, which is executed by the World Health Organization (WHO/TDR), and Wyeth Pharmaceuticals. The work ranges from the development of a formulation for human use and initial studies in healthy volunteers, to clinical studies and community studies in Africa.

WHO/TDR, working in partnership with African investigators and institutions, is building capacity and managing the conduct of clinical trials conducted in Africa. If the development is successful and results in a positive scientific opinion from the European Medicines Evaluation Agency (EMEA), the manufacturer will request approval by national regulatory authorities in the countries where onchocerciasis is endemic.

In conducting this trial, TDR will be working with African investigators and institutions. Fifteen hundred people at four sites in Ghana, Liberia and the Democratic Republic of Congo will be enrolled in the study. Preparation has been ongoing since 2007 and included building a clinical research centre in Lofa County, Liberia, and in Nord-Kivu in the Democratic Republic of Congo (DRC). Buildings not used since the war in Ituri, DRC, have been renovated. All centres have been provided with necessary equipment and the research teams trained on how to conduct the trial according to international standards.

The trial will take place over the next two and a half years. Currently, the disease is controlled by ivermectin which has been donated for more than twenty years by the pharmaceutical company Merck & Co. Inc. for use in onchocerciasis endemic countries. Treatment with ivermectin has enabled significant progress in the control of onchocerciasis, and currently reaches more than 60 million people in Africa annually. However, ivermectin kills the *O. volvulus* larvae but not the adult worms, so annual treatments for an extended period of time (at least 11–14 years) are required to ensure disease control.

If moxidectin kills not only the larvae but also sterilizes or kills the adult worms, it has the potential to interrupt the disease transmission cycle within around six annual rounds of treatment. The medicine could be distributed through community-directed mechanisms set up in collaboration among APOC, African control programmes, and NGOs for the distribution of ivermectin.

Reference: World Health Organization. Moxidectin could dramatically speed up elimination of disease across Africa. *Press release*, 1 July 2009 at http://apps.who.int/tdr/svc/news-events/news/phase3-trial-moxidectin

Malaria: evaluation of rapid diagnostic tests

The largest-ever independent, laboratory-based evaluation of rapid diagnostic tests (RDTs) for malaria has shown that some tests on the market perform exceptionally well in tropical temperatures and can detect even low parasite densities in blood samples, while other tests were only able to detect the parasite at high parasite densities.

The evaluation was co-sponsored by the WHO Regional Office for the Western Pacific (WPRO), WHO-based Special Programme for Research and Training in Tropical Diseases (TDR) and the Foundation for Innovative New Diagnostics (FIND). Testing was performed at the US Centers for Disease Control and Prevention (CDC). Forty-one commercially available RDTs went through a blinded laboratory evaluation.

The findings will serve as a tool for countries to make informed choices from among the dozens of tests commercially available and on the purchase and use of rapid diagnostics that are best suited to local conditions. This performance evaluation will also inform procurement and prioritization for diagnostic test entry into the WHO Prequalification Diagnostics Programme and WHO Procurement Schemes. Donor agencies also regularly refer to WHO recommendations on diagnostics when making their own purchases.

In addition to product testing FIND , TDR and WHO have also collaborated to establish procedures and quality assured facilities for routine lot testing of rapid diagnostics in Asia and Africa. Evaluation of malaria diagnostic tests by WHO and partners has found variation in test performance.

During the evaluation, samples of blood from patients infected with *P. falciparum* and *P. vivax* in diverse geographic locations were diluted to achieve both a low parasite density and high parasite densities . At low parasite density, samples were tested against two rapid tests per lot (2 lots) and at high parasite density samples were tested against one rapid test per lot (2 lots).

Conclusions from the findings:

- Several RDTs demonstrated consistent detection of malaria at low parasite densities, have low false-positive rates, are stable at tropical temperatures, are relatively easy to use, and can detect P*. falciparum, P. vivax* infections, or both.
- Performance between products varied widely at low parasite density (200 parasites/microlitre); however, most products showed a high level of detection at 2000 to 5000 parasites/microlitre.
- *P. falciparum* tests targeting the histidine rich protein 2 (HRP2) antigen demonstrated the highest detection rates, but some tests targeting Plasmodium lactate dehydrogenase (pLDH) also exhibited high detection rates.
- Test performance varied between lots, and widely between similar products, confirming the advisability of lot testing post-purchase and prior to use in the field.
- The results highlight the need for manufacturers to have adequate reference materials for product development and lot-release. The WHO-FIND Malaria RDT Evaluation Programme, in collaboration with the CDC, will soon offer quality standard panels to manufacturers to assist in this process.

A second round of performance evaluations for 29 products is currently being carried out by TDR, FIND and CDC, with results due to be published in 2010. An executive summary of findings along with the detailed evaluation of test performance results are provided in the report available online at http://www.who.int/tdr.

References

1. Special Programme for Research & Training in Tropical Diseases (TDR). *News Release,* 24 April 2009 at http://www.who.int/tdr

2. Foundation for Innovative New Diagnostics (FIND) at http://www.finddiagnostics.org

ATC/DDD Classification

ATC/DDD Classification (Temporary)

The following anatomical therapeutic chemical (ATC) classifications and defined daily doses (DDDs) were agreed by the WHO International Working Group for Drug Statistics Methodology, 24 March 2009. Comments or objections to the decisions from the meeting should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology at whocc@fhi.no. If no objections are received, the new ATC codes and DDDs will be considered final and included in the January 2010 issue of the ATC index.The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy.

ATC level	INN/Common name	ATC code
New ATC level codes (other than 5th level):		
Agents for atopic dermatitis, excluding corticosteroids		D11AH
Angiotensin II antagonists, other combinations		C09DX
Other blood products		B05AX
Other throat preparations		R02AX
New ATC 5th level codes:		
	alfuzosin and finasteride	G04CA51
	alogliptin	A10BH04
	bendamustine	L01AA09
	biapenem	J01DH05
	bisoprolol, combinations	C07AB57
	blood plasma	B05AX03
	canakinumab	L04AC08
	carisbamate	N03AX19
	cefozopran	J01DE03
	cholic acid	A05AA03
	dapoxetine	G04BX14
	denosumab	M05BX04
	erythrocytes	B05AX01
	fluoromethylcholine (^{18}F)	V09IX07
	flurbiprofen	R02AX01
	indacaterol	R03AC18
	iodine (^{124}I) 2beta-carbomethoxy-3beta-(4iodophenyl)-tropane	V09AX02
	maribavir	J05AX10
	nomegestrol and estrogen	G03AA14
	ofatumumab	L01XC10

ATC level	INN/Common name	ATC code
	ofloxacin	S02AA16
	pioglitazone and alogliptin	A10BD09
	prasugrel	B01AC22
	pravastatin and fenofibrate	C10BA03
	sodium iodide (^{124}I)	V09FX04
	stem cells from umbilical cord blood	B05AX04
	tapentadol	N02AX06
	telmisartan and amlodipine	C09DB04
	thrombocytes	B05AX02
	valsartan, amlodipine and hydrochlorothiazide	C09DX01
	valsartan and aliskiren	C09DX02

INN/Common name	Previous ATC code	New ATC code
ATC code changes:		
cromoglicic acid	D11AX17	D11AH03
pimecrolimus	D11AX15	D11AH02
tacrolimus	D11AX14	D11AH01

Previous name	New name	New ATC code
ATC name changes:		
hydroxybutyric acid	sodium oxybate	N01AX11
hydroxybutyric acid	sodium oxybate	N07XX04

New DDDs:

INN/common name	DDD	Unit	Adm.R	ATC code
alitretinoin	20	mg	O	D11AX19
biapenem	1.2	g	P	J01DH05
cefozopran	4	g	P	J01DE03
dapoxetine	30	mg	O	G04BX14
degarelix	2.7	mg	P	L02BX02
etravirine	0.4	g	O	J05AG04
flurbiprofen	44	mg	O	R02AX01
lacosamide	0.3	g	O,P	N03AX18
prasugrel	10	mg	O	B01AC22
rivaroxaban	10	mg	O	B01AX06
ustekinumab	0.54	mg	P	L04AC05

ATC/DDD Classification

ATC/DDD Classification (Final)

The following anatomical therapeutic chemical (ATC) classifications and defined daily doses (DDDs) were agreed by the WHO International Working Group for Drug Statistics Methodology in October 2008. They will be included in the January 2010 issue of the ATC index. The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy. The WHO Collaborating Centre for Drug Statistics Methodology can be contacted at whocc@fhi.no

ATC level	INN/Common name	ATC code
New ATC level codes (other than 5th level):		
Peripheral opioid receptor antagonists		A06AH
New ATC 5th level codes:		
	aciclovir, combinations	D06BB53
	alvimopan	A06AH02
	asenapine	N05AH05
	bacitracin	J01XX10
	bazedoxifene	G03XC02
	becaplermin	A01AD08
	benzethonium chloride	D08AJ08
	bromfenac	S01BC11
	casopitant	A04AD13
	cefcapene	J01DD17
	cevimeline	N07AX03
	cilostazol	C04AX33
	corifollitropin alfa	G03GA09
	dalbavancin	J01XA04
	dapsone	D10AX05
	dexmethylphenidate	N06BA11
	doxercalciferol	H05BX03
	eltrombopag	B02BX05
	eperisone	M03BX09
	everolimus	L01XE10
	fluocinolone acetonide	S02BA08
	golimumab	L04AB06
	iclaprim	J01EA03
	lansoprazole, amoxicillin and clarithromycin	A02BD0
	lisinopril and amlodipine	C09BB03

ATC level	INN/Common name	ATC code
	meningococcus, tetravalent purified polysaccharide antigen conjugated	J07AH08
	meptazinol	N02AX05
	methylnaltrexone bromide	A06AH01
	mitiglinide	A10BX08
	nabiximols	N02BG10
	nalfurafine	V03AX01
	oritavancin	J01XA05
	pazopanib	L01XE11
	pegloticase	M04AX02
	phenazone	S02DA03
	potassium acetate	B05XA17
	pralatrexate	L01BA05
	regadenoson	C01EB21
	saxagliptin	A10BH03
	silodosin	G04CA04
	sodium fluoride (^{18}F)	V09IX06
	sodium levofolinate	V03AF10
	stavudine, lamivudine and nevirapine	J05AR07
	tamsulosin and dutasteride	G04CA52
	vinflunine	L01CA05

INN/Common name	Previous ATC code	New ATC code
ATC code changes:		
clotiapine	N05AX09	N05AH06
paricalcitol	A11CC07	H05BX02

** Please note that the changes will not be implemented before January 2010*

Previous name	New name	New ATC code
ATC name changes:		
Diazepines, oxazepines and thiazepines	Diazepines, oxazepines, thiazepines and oxepines	N05AH

New DDDs:

INN/common name	DDD	Unit	Adm.R	ATC code
cefcapene	0.45	g	O	J01DD17
cefotiam	1.2	g	O	J01DC07
cevimeline	90	mg	O	N07AX03
cilostazol	0.2	g	O	C04AX33
dabigatran etexilate	0.22	g	O	B01AE07
doripenem	1.5	g	P	J01DH04
eperisone	0.15	g	O	M03BX09
febuxostat	80	mg	O	M04AA03
icatibant	30	mg	P	C01EB19
meptazinol	1.2	g	O,P	N02AX05
methylnaltrexone bromide	6	mg	P	A06AH01
micafungin	0.1	g	P	J02AX05
mitiglinide	30	mg	O	A10BX08
polymyxin B	3	MU	O	A07AA05
rilonacept	23	mg	P	L04AC04
romiplostim	30	mcg	P	B02BX04
sodium levofolinate	30	mg[1)]	P	V03AF10
tafluprost	0.3	ml[2)]		S01EE05

(1) Expressed as levofolinic acid
(2) Single dose package

Change of DDDs

INN/common name	Previous DDD	New temporary DDD	ATC Code
Risperidone*	1.8 mg P depot	2.7 mg P depot	N05AX08

** Please note that the changes will not be implemented before January 2010*

Recent Publications, Information and Events

Good clinical laboratory practices

In 2006, WHO/TDR convened a meeting of organizations engaged in clinical trials in disease endemic countries to discuss the applicability of Good clinical laboratory practices (GCLP) guidelines to their work. It was agreed that GCLP would be a valuable tool for improving quality laboratory practice. In line with that agreement, WHO/TDR recently acquired copyright to GCLP guidelines that were originally published in 2003 by a working party of the Clinical Committee of the British Association of Research Quality Assurance (BARQA), with the aim of disseminating them widely in developing countries and developing related training materials. Compliance with GCLP guidelines will allow clinical laboratories to ensure that safety and efficacy data is repeatable, reliable, auditable and easily reconstructed in a research setting. Additionally, GCLP guidelines set a standard for compliance by laboratories involved in the analysis of samples from TDR-supported clinical trials.

Reference: Special Programme for Research & Training in Tropical Diseases (TDR). Good Clinical Laboratory Practice (GCLP). DOI: 10.2471/TDR.09.978-924-1597852. 13 March 2009 at http://www.who.int/tdr

Laboratory diagnostic tools for tuberculosis control

There is currently a lack of information available to national tuberculosis programmes and funding and technical agencies on new TB diagnostic tools under development and in implementation. With this in mind, *New laboratory diagnostic tools for tuberculosis control* describes 19 new or improved diagnostic tools from many initiatives under way worldwide. Three of the tools described in this document have already been endorsed by WHO and are being implemented by countries, while others are still under development or in the pilot phase and expected to be ready for use in the coming years.

The brochure stands in as an interim document until a more complete blueprint of current R&D efforts can be developed. The purpose is not to recommend specific tools, but rather to provide summary information about tools being developed and becoming available so that all who play a part in TB control, especially in national TB programmes, can make well-informed decisions when retooling.

Reference: Stop TB Partnership: Retooling Task Force and New Diagnostic Working Group at http://apps.who.int/tdr/svc/publications/non-tdr-publications/diagnostic-tool-tb

WorldPharma2010: clinical pharmacology

The 16th World Congress on Basic and Clinical Pharmacology will be held from 17–23 July 2010 in Copenhagen, Denmark

The WorldPharma2010 event will include a two-day focused conference on Clinical pharmacology in emerging countries. Other sessions will include:

- Addiction and doping: neurobiological and clinical basis of emerging treatments.

- Developments in treatment of sexual dysfunction and diseases of the lower urinary tract.
- Drugs for half the world: paediatric clinical pharmacology.
- Endothelium in health and disease.
- G protein-coupled 7TM receptors: from molecular to physiological function.
- Inflammation and immunopharmacology: new tools for old diseases.
- Ion channelopathies: new windows on complex disease and therapy.
- Ion channels in analgesia and anaesthesia.
- Maximizing benefits and minimizing harm from drugs.
- Natural products: past and future?
- New approaches and targets in psychiatry.
- Nuclear receptor targets for treatment of diseases.
- Pharmacoepidemiology, current controversies and opportunities.
- Simulation and data modelling in drug development. Better drugs faster?
- The heart gone wrong; stabilization of cardiac function.
- Translational science in the metabolic syndrome.
- Transmembrane transport: perspectives for disease and drug discovery.

Reference: http://www.WorldPharma2010.org

Ethical guidelines for epidemiology

The newly published and revised CIOMS *International Ethical Guidelines for Epidemiological Studies* are intended to draw the attention of investigators, sponsors and ethical review committees to the need to consider carefully the ethical implications of research protocols and the manner in which research is conducted in order to attain high scientific and ethical standards in epidemiological studies and research.

Reference: Council for International organizations of Medical Sciences (CIOMS) at http://www.cioms.ch

Dengue: evaluation of immunoglobulin M tests

Dengue infection can produce a broad spectrum of symptoms and range from mild febrile illness to severe disease. Clinical features are often nonspecific and therefore require laboratory confirmation. Accurate but sophisticated methods, including virus isolation or polymerase chain reaction (PCR), require advanced equipment and infrastructure.

Serological assays that can detect specific immunoglobulin M (IgM) or immunoglobulin G (IgG) antibodies to dengue virus are widely available. These assays can provide an alternative to virus isolation or PCR to support the diagnosis of dengue fever. First-time (primary) dengue virus infections typically have a stronger and more specific IgM response and subsequent (secondary) infections show a weaker IgM response but a strong IgG response. These differing IgM response patterns to infection underscore the need to evaluate the sensitivity and specificity of commercially available tests, especially for diagnosis of secondary dengue virus infections.

WHO/TDR and the Paediatric Dengue Vaccine Initiative have collaborated to evaluate commercially available anti-dengue virus IgM diagnostic tests. A network of seven laboratories in Asia and Latin America has been established to carry out the work. *Evaluation of commercially available anti-dengue virus immunoglobulin M tests* describes the results of an evaluation of nine commercially available anti-dengue virus IgM tests, using a panel of well-characterized, archived serum specimens from patients with confirmed dengue virus infections and from patients with other potentially confounding infections and conditions.

Reference: World Health Organization Special Programme for Research & Training in Tropical Diseases (TDR). Evaluation of commercially available anti-dengue virus immunoglobulin M tests. *Diagnostics Evaluation Series No. 3.* at http://www.who.int/tdr

WHO/HAI student manual on pharmaceutical promotion

Medicines are a vital part of improving and maintaining health. Healthcare professionals, such as doctors and pharmacists, play a key role in ensuring that medicines are prescribed and used rationally.

However, numerous concerns have been raised about the relationship between healthcare professionals and the pharmaceutical industry — particularly the industry's influence on prescribing and dispensing decisions. This influence can lead to less than optimal treatment choices and can even be detrimental to patient health.

Research shows that while in training, many healthcare professionals receive little or no instruction on how to assess pharmaceutical promotion and how to understand its often subtle influence on their behaviour. In response, WHO and Health Action International (HAI) have developed a new publication: *Understanding and Responding to Pharmaceutical Promotion – A Practical Guide*. This draft manual can assist educators and healthcare professionals in teaching medical and pharmacy students about pharmaceutical promotion.

Reference: World Health Organization at http://www.who.int/medicines and Health Action International at http://www.haiweb.org