

WHO PHARMACEUTICALS NEWSLETTER



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

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

*Quality Assurance and Safety:
Medicines, EMP-HSS,
World Health Organization,
1211 Geneva 27, Switzerland,
E-mail address: pals@who.int*

*This Newsletter is also available on
our Internet website:
<http://www.who.int/medicines>*

*Further information on adverse
reactions may be obtained from the
WHO Collaborating Centre for
International Drug Monitoring
Box 1051
751 40 Uppsala
Tel: +46-18-65.60.60
Fax: +46-18-65.60.80
E-mail: info@who-umc.org
Internet: <http://www.who-umc.org>*

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In this edition of the WHO Pharmaceuticals Newsletter our readers will find reference to decisions around the world on some old medicines such as dextropropoxyphene, acetaminophene, bisphosphonates and quinine, as well as newer ones such as dolasetron, dronedarone, saquinavir and sitaxentan. Sitaxentan has been withdrawn worldwide by the manufacturer because of unpredictable serious liver injury. Read the background information from Australia, Canada and EMA.

In a feature article of this edition of the Newsletter we continue to give information about WHO's Prequalification of Medicines Programme; this time about inspection of manufacturing sites for Active Pharmaceutical Ingredients (APIs).

A report of the latest meeting (8 – 9 December 2010) of the WHO Global Committee of Vaccine Safety is found as the second feature article of the Newsletter.

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Acetaminophen (Paracetamol INN) prescription products

The maximum amount will be limited to 325 mg per dosage unit; A Boxed Warning will highlight the potential for severe liver failure.

USA. The U.S. Food and Drug Administration (The US FDA) decided to limit the strength of acetaminophen in prescription drug products, which are predominantly combinations of acetaminophen and opioids, to 325 mg per tablet, capsule, or other dosage unit. In addition, a Boxed Warning highlighting the potential for severe liver injury and a Warning highlighting the potential for allergic reactions (swelling of the face, mouth, and throat, difficulty breathing, itching or rash) will be added to the label of all prescription products that contain acetaminophen. The Agency says that these actions will help to reduce the risk of severe liver injury and allergic reactions associated with acetaminophen. Examples of prescription products that contain acetaminophen include hydrocodone with acetaminophen (Vicodin, Lortab), and oxycodone with acetaminophen (Tylox, Percocet). Over-the-counter (OTC) products containing acetaminophen (e.g. Tylenol) are not affected by these actions.

The US FDA advised health-care professionals that severe liver injury, including cases of acute liver failure resulting in liver transplant and death, has been reported with the use of acetaminophen. Rare cases of anaphylaxis and other hypersensitivity reactions have occurred with the use of acetaminophen. Health-care

professionals are also reminded to advise patients not to exceed the acetaminophen maximum total daily dose (four grams/day), and not to drink alcohol while taking acetaminophen-containing medications.

Reference:

MedWatch Safety Information, US FDA, 13 January 2011
(www.fda.gov)

Benzonatate

Accidental ingestion by children

USA. The US FDA has warned the public that accidental ingestion of benzonatate (Tessalon®) by children under the age of 10 years can result in death from overdose. Benzonatate is approved for relief of cough in patients over 10 years of age. The safety and effectiveness of benzonatate in children under 10 years of age have not been established. Therefore, prescribing benzonatate to that age group is not recommended.

The US FDA states that all accidental ingestions reported to the Agency until 19 May 2010 (seven cases) occurred in children less than 10 years of age. Five of the seven accidental ingestions resulted in death in children less than two years of age. Two pediatric patients (ages 12 months and four years) were hospitalized due to accidental benzonatate ingestion and survived the event. Overdose with benzonatate in children less than two years of age has been reported following accidental ingestion of as few as one or two capsules. Individuals who experience overdose of benzonatate may exhibit restlessness, tremors,

convulsions, coma, and cardiac arrest.

Signs and symptoms of benzonatate overdose have been reported within 15 to 20 minutes and death has been reported within hours of ingestion.

The US FDA advises patients to keep benzonatate in a child-resistant container and to store it out of reach of children. The Agency also advises parents and caretakers to seek medical attention immediately if a child accidentally ingests benzonatate. The US FDA is revising the benzonatate drug label to warn about accidental ingestion resulting in overdose and death in children below the age of 10 years.

Reference:

FDA Drug Safety Communication, US FDA, 14 December 2010
(www.fda.gov)

Bevacizumab

Withdrawal of authorization of combination with docetaxel for breast cancer treatment in Europe; removal of breast cancer indication in the USA

Europe (1). The European Medicines Agency (EMA) has confirmed that the benefits of bevacizumab (Avastin®) in combination with paclitaxel outweigh its risks and that this combination remains a valuable treatment option for patients suffering from metastatic breast cancer. The Agency's Committee for Medicinal Products for Human Use (CHMP) also concluded that the balance of benefits and risks of bevacizumab in combination with docetaxel is negative and that this combination should no longer be used in the treatment of breast cancer. Bevacizumab is used in combination with other anticancer medicines to treat cancers of the colon, rectum, lung, kidney or breast that are either advanced or metastatic.

The EMA explains that the CHMP started a review of the use of bevacizumab in the treatment of metastatic breast cancer because new data from a study suggested that bevacizumab in combination with docetaxel may have a negative impact on the overall survival. The study was submitted to the Agency to support an application to extend the breast cancer indication to include combination therapy with capecitabine. The Agency says that the new data add uncertainty about the effect on overall survival and that a detrimental effect on overall survival cannot be excluded.

The new data also question the size of the effect on progression-free survival, which appears to be smaller than previously observed. Because the increase of progression-free survival remains very small, the CHMP concluded that the benefits of bevacizumab in combination with docetaxel no longer outweigh its risks, and that the authorisation for this combination treatment should be withdrawn.

For bevacizumab in combination with capecitabine, the CHMP adopted a negative opinion on the proposed new indication for metastatic breast cancer, because the relatively modest benefits were considered not to outweigh the high toxicity of this combination, given that the proposed new indication was aimed at patients for whom a relatively mild treatment would be appropriate.

For bevacizumab in combination with paclitaxel, the CHMP concluded that the benefits continue to outweigh the risks, because the available data have been shown to prolong progression-free survival of breast cancer patients without a negative effect on the overall survival.

Therefore, the CHMP recommended that for the treatment of breast cancer, bevacizumab should only be used in combination with paclitaxel. This recommendation does not affect the other indications than breast cancer.

USA (2). The US FDA has recommended removing the breast cancer indication for bevacizumab (Avastin®) because the medicine has not been shown to be safe and effective for that use. This recommendation will not affect the approvals for colon, kidney, brain, and lung cancers.

The decision has been made after the Agency reviewed the results of four clinical studies of bevacizumab in women with breast cancer and determined that the data indicate that the medicine does not prolong overall survival in breast cancer patients or provide a sufficient benefit in slowing disease progression to outweigh the significant risk to patients. The US FDA states that none of the studies demonstrated that patients receiving bevacizumab lived longer, and that patients receiving bevacizumab experienced a significant increase in serious side effects. These risks include severe high blood pressure; bleeding and haemorrhage; the development of perforations in the body, including in the nose, stomach, and intestines; and heart attack or heart failure.

The US FDA advises that oncologists currently treating patients with bevacizumab for metastatic breast cancer should use their medical judgment when deciding whether a patient should continue treatment with the medicine or consider other therapeutic options.

Bevacizumab was approved in combination with chemotherapy (paclitaxel) in February 2008 under the FDA's accelerated approval program. The US FDA explains that the data submitted after the accelerated approval showed only a small effect on "progression-free survival" without evidence of an improvement in overall survival or a clinical benefit to patients sufficient to outweigh the risks. The small increase in "progression-free survival" reflects a small, temporary effect in slowing tumour growth. The Agency says that bevacizumab has also been associated with several other serious and potentially life-threatening side effects

including the risk of stroke, wound healing complications, organ damage or failure; and the development of a neurological condition called reversible posterior leukoencephalopathy syndrome. On the basis of all available data relating to the use of bevacizumab (Avastin) to treat metastatic breast cancer, the Agency has determined that the risks of the medicine outweigh the benefits for this use.

Reports in WHO Global ICSR database, Vigibase:

Bevacizumab

Total number of reports:
10,047

Number of reactions similar to those mentioned in communication from US FDA:

| | |
|--------------------------|-----|
| Nasal septum perforation | 37 |
| Intestinal perforation | 413 |
| Circulatory failure | 34 |
| Cardiac failure | 219 |
| Hypertension pulmonary | 39 |
| Hypertension | 512 |
| Hypotension | 261 |
| Myocardial infarction | 172 |
| Haemorrhage NOS | 106 |
| Prothrombin decreased | 90 |
| Embolism pulmonary | 410 |
| Thrombocytopenia | 338 |
| Thrombosis | 117 |

References:

(1) Press release, Questions and answers, EMA, 16 December 2010 (www.ema.europa.eu).

(2) MedWatch Safety Information, US FDA, 16 December 2010 (www.fda.gov)

Bisphosphonate

Safety measures against osteonecrosis and osteomyelitis of jaw

Japan (1). The Ministry of Health, Labour and Welfare (MHLW), Japan decided to alert health-care professionals to the risk of osteonecrosis of jaw associated with oral formulations of bisphosphonates (BPs) (alendronate, etidronate, risedronate), in addition to BP injections, for which the MHLW had issued an alert in October 2006. Bisphosphonates are used as oral medications for treatment of osteoporosis and as injections for treatment of hypercalcaemia of malignancy, bone lesion of multiple myeloma, bone lesion from bone metastasis of solid carcinoma, and osteolytic bone metastasis of breast cancer.

Based on the epidemiological studies on oral BP and reports of adverse events in Japan, the MHLW concluded that safety measures equivalent to those for BP injections should be taken for oral BPs to prevent osteonecrosis and osteomyelitis of jaw. In June 2010, the MHLW required manufacturers to revise the package inserts of BP products to include the following descriptions.

- Administration of BPs may increase possible risks of osteonecrosis and osteomyelitis of jaw regardless of the route of administration. The risk may be higher in patients treated with BP injections.
- Physicians need to advise patients of the following: to receive appropriate dental examinations before using BPs and, if necessary, to have planned invasive dental procedures such as tooth extraction done before

treatment, as well as to receive periodic dental checkups and to avoid invasive dental procedures in the jaw bone, such as tooth extraction, during treatment.

According to the MHLW, approximately 80 to 100 cases of osteonecrosis and osteomyelitis of jaw have been reported as adverse drug reactions (ADRs) of oral BPs annually. A detailed review of reports showed that some patients had received dental procedures such as tooth extraction by dentists who had been unaware of the treatment.

There were also patients who had failed to maintain oral hygiene while taking BP. From 2007 to 2009, osteonecrosis and osteomyelitis of jaw were reported as ADRs as follows (numbers of ADR cases (numbers of ADRs)).

Alendronate sodium hydrate (oral dosage form): 197 (238)

Etidronate disodium (oral dosage form): seven (eight)

Sodium risedronate hydrate (oral dosage form): 61 (64)

In addition, the manufacturers were required to prepare and distribute patient cards for BP users to help health-care professionals inform patients of precautions concerning BP use, as well as for their use of BP to be known at dental or oral surgery services.

(See WHO Pharmaceuticals Newsletters No. 1, 2010, No. 1, 2008, No.5, 2006 and No.6, 2004 for a review on the risk of osteonecrosis of the jaw in Europe, for alert on musculoskeletal pain in USA, reports of osteonecrosis of the jaw in Australia, and reports of osteonecrosis of the jaw in USA, respectively.)

UK (2). The Medicines and Healthcare products Regulatory Agency (MHRA) advised that treatment with bevacizumab or sunitinib, which are used to treat certain cancers, may be a risk factor for the development of osteonecrosis of the jaw (ONJ), particularly if a patient has previously received, or is treated concurrently with, bisphosphonates. Health-care professionals are advised that dental examination and appropriate preventive dentistry should be considered before treatment with bevacizumab or sunitinib. Invasive dental procedures should be avoided, if possible, in patients treated with bevacizumab or sunitinib who have previously received, or who are receiving, intravenous bisphosphonates.

According to the Drug Safety Update, cases of ONJ have been reported in patients with cancer in association with treatment with bevacizumab or sunitinib, most of whom had received previous or concomitant treatment with intravenous bisphosphonates. The MHRA states that there is sufficient evidence to suspect that bevacizumab and sunitinib may independently increase the risk of ONJ.

References:

(1) *Pharmaceuticals and Medical Devices Safety Information No.272, MHLW, September 2010* (www.pmda.go.jp/english).

(2) *Drug Safety Update, January 2011, Volume 4, Issue 6, A1, MHRA* (www.mhra.gov.uk).

Dextropropoxyphene

Recall and withdrawal due to risk of abnormal heart rhythms

Canada. Health Canada and Paladin Labs Inc announced that the company has decided to voluntarily recall and withdraw dextropropoxyphene (Darvon-N) on the Canadian market and discontinue the sale of the product.

Dextropropoxyphene is an opioid pain reliever used to treat mild to moderate pain.

The company states that results of a new study show that, even at therapeutic doses, dextropropoxyphene can significantly prolong the PR interval, widen the QRS complex, prolong the QT interval and therefore increase the risk of serious abnormal heart rhythms. Elderly patients and those with renal insufficiency may be especially susceptible to the proarrhythmic effects of dextropropoxyphene. Health-care professionals are advised to stop prescribing and dispensing dextropropoxyphene (Darvon-N) to patients, and to be aware of the possible risk of cardiac conduction abnormalities in patients taking this medicine and assess patients for these events if they present with any signs or symptoms of arrhythmia.

(See WHO *Pharmaceuticals Newsletters* No. 6, 2010, No.4, 2010 and No. 4, 2009 for withdrawal of dextropropoxyphene in the USA, New Zealand and Europe as well as reports in WHO Global ICSR database.)

Reference:

Advisories, Warnings and Recalls, Health Canada, 1 December 2010 (www.hc-sc.gc.ca).

Dolasetron mesylate

Reports of abnormal heart rhythms

USA. The US FDA notified health-care professionals that the injection form of dolasetron mesylate (Anzemet®) should no longer be used to prevent chemotherapy induced nausea and vomiting (CINV) in paediatric and adult patients. A contraindication against this use is being added to the product label for dolasetron mesylate injection. The Agency warns that new data demonstrate that dolasetron mesylate injection can increase the risk of developing torsade de pointes, which can be fatal. Patients at particular risk are those with underlying heart conditions or those who have existing heart rate or rhythm problems.

The US FDA advises the following:

- Dolasetron mesylate should not be used in patients with congenital long-QT syndrome.
- Hypokalemia and hypomagnesemia should be corrected before administering dolasetron mesylate. These electrolytes should be monitored after administration as clinically indicated.
- Electrocardiogram monitoring should be used in patients with congestive heart failure, bradycardia or underlying heart disease, the elderly and patients who are renally impaired.
- Dolasetron mesylate causes dose-dependent prolongation in the QT, PR and QRS intervals. Medicines known to prolong the PR interval (such as verapamil) or QRS interval

(such as flecainide or quinidine) should be avoided in patients taking dolasetron mesylate.

Dolasetron mesylate injection may still be used for the prevention and treatment of postoperative nausea and vomiting because the lower doses used are less likely to affect the electrical activity of the heart and result in abnormal heart rhythms. Dolasetron mesylate tablets may still be used to prevent CINV because the risk of developing an abnormal heart rhythm with the oral form of this medicine is less than that seen with the injection form. However, the US FDA states that a stronger warning about this potential risk is being added to the product label for dolasetron mesylate tablets.

Reports in WHO Global ICSR database, Vigibase:

Dolasetron

Number of reports (System Organ Class – Heart Rate and Rhythm Disorders): 36

Reported reactions (number of events):

| | |
|-------------------------------------|----|
| <i>Palpitation</i> | 5 |
| <i>Tachycardia</i> | 20 |
| <i>Tachycardia supraventricular</i> | 7 |
| <i>Tachycardia ventricular</i> | 6 |
| <i>Torsade de pointes</i> | 2 |

Reference:

FDA Drug Safety Communication, US FDA, 17 December 2010 (www.fda.gov)

Dronedarone

Risk of severe liver injury

Europe (1). The EMA announced that the Agency's Committee for Medicinal Products for Human Use (CHMP) is reviewing all available data concerning the possible risks of liver injury associated with the use of the anti-arrhythmic medicine dronedarone (Multaq®) and their impact on its benefit-risk balance. The CHMP has become aware of reports of severe liver injury in patients treated with the medicine, including two cases of liver failure requiring a transplant, which were reported in December 2010. The two cases occurred four, five and six months after starting treatment in patients with normal liver function before treatment.

The CHMP noted that although the two patients requiring a liver transplant were also taking other medications, a causal relationship with dronedarone could not be excluded. Therefore, the CHMP concluded that there was a need for an urgent regulatory action to help manage the possible risk of severe liver complications with the medicine. The Committee recommended that warnings and precautions be introduced into the medicine's prescribing information, to ensure that patients' liver function is tested before initiation of treatment, closely monitored during treatment, and treatment is stopped if there are signs of potential liver damage. Health-care professionals are advised that:

- Before starting treatment with dronedarone, doctors should perform liver function tests. Tests should be repeated monthly for six months, at months 9 and

12, and periodically thereafter.

- Doctors should contact patients who are currently receiving dronedarone so that liver function tests can be performed. Thereafter, they should carry out further tests as described above depending on when treatment was started.
- Doctors should stop treatment with dronedarone in patients with raised levels of the liver enzyme alanine aminotransferase (more than three times above the upper limit of normal). Appropriate investigation and close observation of patients should continue until the enzyme levels return to normal.

USA (2). The US FDA has warned that the Agency has received several case reports of hepatocellular liver injury and hepatic failure in patients treated with dronedarone (Multaq®), including two post-marketing reports of acute hepatic failure requiring transplantation. Information about the potential risk of liver injury from dronedarone is being added to the dronedarone labels. Dronedarone is used to treat abnormal heart rhythm in patients who have had an abnormal heart rhythm (atrial fibrillation or atrial flutter) during the past six months. Dronedarone can reduce the risk of being hospitalized for these heart problems. Dronedarone was approved with a Risk Evaluation and Mitigation Strategy, to prevent its use in patients with severe heart failure or who have recently been in the hospital for heart failure. The Agency says that in a study of patients with these conditions, patients given dronedarone had a greater than two-fold increase in risk of death.

Health-care professionals are reminded to advise patients to contact a health-care professional immediately if they experience signs and symptoms of hepatic injury or toxicity (anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant pain, jaundice, dark urine, or itching) while taking dronedarone. The US FDA recommends health-care professionals to consider obtaining periodic hepatic serum enzymes, especially during the first six months of treatment. If hepatic injury is suspected, dronedarone should be promptly discontinued and testing of serum liver enzymes and bilirubin should be performed.

Reports in WHO Global ICSR database, Vigibase:

Dronedarone

Number of reports (System Organ Class – Liver and Biliary System Disorders): 44

Most reported reactions (number of events):

| | |
|---------------------------|----|
| Hepatic enzymes increased | 13 |
| SGOT increased | 9 |
| SGPT increased | 11 |
| Gamma-GT increased | 8 |
| Hepatic function abnormal | 15 |
| Hepatitis | 8 |
| Hepatitis cholestatic | 7 |
| Bilirubinaemia | 6 |

References:

(1) News, Questions and answers, EMA, 21 January 2011 (www.ema.europa.eu).

(2) FDA Drug Safety Communication, US FDA, 14 January 2011 (www.fda.gov)

Insulin combined with pioglitazone

Risk of cardiac failure

UK. The MHRA warned that cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for the development of cardiac failure. Health-care professionals are advised that if the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. The product information for pioglitazone already contains warnings about its use in combination with insulin. Warnings are also being added to the product information for all insulin products.

Reference:

Drug Safety Update, January 2011, Volume 4, Issue 6, A2, MHRA (www.mhra.gov.uk).

Quinine

Not indicated for nocturnal leg cramps

New Zealand. The New Zealand Medicines and Medical Devices Safety Authority (Medsafe) has reminded prescribers that quinine is no longer indicated for the treatment of leg cramps in New Zealand, after CARM continues to receive reports of adverse events associated with the use of quinine for leg cramps. In New Zealand, a review on the safety of quinine was conducted in 2006 following reports of thrombocytopenia, and concluded that the benefit-risk profile of quinine no longer supported an indication for the treatment of leg cramps. Subsequently, the indication for

prevention and treatment of nocturnal leg cramps was removed from quinine containing products in 2007. Quinine is now only indicated for the treatment of malaria and myotonia.

(See Newsletter No. 4, 2010 for warning against the routine use for nocturnal leg cramps in the UK and new risk management plan in the USA)

Reference:

Prescriber Update Vol. 31, No.4 December 2010 (www.medsafe.govt.nz).

Saquinavir

Update on potential risk of arrhythmia

UK. The MHRA has advised that antiretroviral-treatment-naïve patients should start saquinavir at a reduced dose for the first week of treatment because of the risk of QT and PR prolongation. Saquinavir (Invirase®) is a protease inhibitor indicated in combination with ritonavir and other antiretroviral drugs for treatment of HIV infection. The standard dose of saquinavir/ritonavir in adults and adolescents older than 16 years is 1000 mg/100 mg twice daily. Saquinavir is contraindicated in patients at high risk of arrhythmia, and in patients using other medicines that may cause QT or PR prolongation, such as the other protease inhibitors atazanavir and lopinavir, and methadone.

Baseline and follow-up electrocardiogram recording in patients taking concomitant drugs known to increase the plasma levels of saquinavir is also recommended (e.g. potent inhibitors of the cytochrome p450 3A4 enzyme such as the protease inhibitor nelfinavir, the

antifungal itraconazole, and proton pump inhibitors such as omeprazole).

According to the recommendations by the European Medicines Agency's Committee for Medicinal Products for Human Use, the MHRA advised that half the standard dose of saquinavir (i.e. 500 mg saquinavir plus 100 mg ritonavir, twice daily) should be used for the first week of therapy. The benefits of saquinavir in the authorised indication continue to outweigh the risks.

Health-care professionals are advised that saquinavir should not be used in patients with congenital or acquired QT prolongation, or other predisposing conditions for cardiac arrhythmias, including concurrent therapy with other drugs that prolong the QT and/or PR interval. In addition, saquinavir should not be used with drugs known to increase the plasma level of saquinavir. In all patients starting saquinavir, electrocardiography should be done before initiating treatment, and after approximately three to four days of therapy. Health-care professionals are also advised to discontinue saquinavir if patients develop: QT prolongation of >480 milliseconds or >20 milliseconds from pre-treatment measurement; PR prolongation; or arrhythmias.

(See Newsletter No.6, 2010 for changes to prescribing information about risk of QT and PR interval prolongation in Europe, Canada and the USA as well as reports in WHO Global ICSR database.)

Reference:

Drug Safety Update, December 2010, Volume 4, Issue 5, A1, MHRA (www.mhra.gov.uk).

Sibutramine

Withdrawal in New Zealand

New Zealand. The consent to distribute sibutramine containing medicines was revoked in New Zealand on 14 October 2010, following a review on preliminary results of the Sibutramine Cardiovascular Outcome Trial (SCOUT). The SCOUT study suggests that subjects treated with sibutramine had an increased risk of non-fatal myocardial infarction and non-fatal stroke compared to those given placebo. Medsafe has advised patients to stop taking sibutramine (Reductil®) and to talk to a health-care professional about alternative weight loss measures and maintenance programmes.

(See WHO Pharmaceuticals Newsletter No.1, 2010 for suspension of marketing authorizations in the European Union and reports in WHO Global ICSR database, and WHO Pharmaceuticals Newsletter No.6, 2010 for market withdrawal in Australia, Canada and the USA.)

Reference:

Prescriber Update Vol. 31, No.4 December 2010, (www.medsafe.govt.nz).

Sitaxentan

Worldwide withdrawal due to cases of unpredictable serious liver injury

Australia (1). The Therapeutic Goods Administration (TGA) notified the public that the supply of sitaxentan (Thelin®) will be suspended in Australia, following Pfizer's announcement that it will withdraw sitaxentan from the market globally. Sitaxentan is used to treat pulmonary hypertension. The TGA advises that patients currently taking sitaxentan should contact their treating doctor as soon as possible to organise the supply of a different medicine, and that patients should not cease their use of this medicine until they have been assessed by their treating doctor and switched to another medicine.

The TGA states that this action has been taken in response to a review of safety data in clinical trials being undertaken overseas that showed patients were at risk of acute liver failure that in some cases was not reversible. The TGA has received 10 adverse event reports of abnormal liver function in Australian patients receiving sitaxentan. The Product Information for sitaxentan contained a boxed warning of the risk of liver side effects and the use of sitaxentan was contra-indicated in patients with pre-existing liver disease.

Canada (2). Pfizer Canada and Health Canada informed health-care professionals and the public that sitaxentan sodium (Thelin®) tablets will be withdrawn from the Canadian market due to concerns about hepatotoxicity. Based on a review of available information,

including new information on two fatalities associated with hepatic injury (a 2009 post-marketing case in the United Kingdom and in a 2010 clinical trial case in a United States registration program at a study site in India), the company concluded:

- Hepatotoxicity is a known risk of sitaxsentan sodium and all endothelin receptor antagonists.
- A newly identified idiosyncratic pattern of liver injury cannot be excluded at this time as a potential risk of sitaxsentan sodium use.
- This idiosyncratic hepatotoxicity does not appear to be associated with identifiable risk factors, does not appear likely to be detected by routine monitoring and, at least in some cases does not appear to resolve with the discontinuation of sitaxsentan sodium.
- The overall benefit of this medicine no longer outweighs the risk in the general population of patients with pulmonary arterial hypertension.

Europe (3). The EMA has been informed of Pfizer's decision to voluntarily withdraw sitaxentan (Thelin®) from worldwide markets and to discontinue all ongoing clinical trials, in response to new information on fatal liver injury. The CHMP reviewed the data on liver toxicity, including three cases of fatal liver injury. One of the cases occurred in the United Kingdom in 2009 and two during clinical trials in India and Ukraine in 2010. Two of the cases of fatal liver injury were causally related to sitaxentan.

The EMA says that the new data suggest that serious hepatic toxicity cannot be prevented in

all patients. The cases were not associated with identifiable risk factors, could not be detected by frequent monitoring and did not resolve with the discontinuation of sitaxentan.

The CHMP noted that alternative treatment options are available, including two other centrally authorised endothelin receptor antagonists (ERAs), bosentan (Tracleer®) and ambrisentan (Volibris®).

The Committee is now starting a review of the hepatotoxic profile of these ERAs to confirm that they remain a valuable option in the treatment of pulmonary hypertension. While this review is ongoing, the CHMP recommends that when choosing alternatives, prescribers should follow treatment guidelines.

References:

(1) *Safety information, Alerts/advisories, TGA, 10 December 2010*
(www.tga.gov.au).

(2) *Advisories, Warnings and Recalls, Health Canada, 20 December 2010*
(www.hc-sc.gc.ca).

(3) *Press releases, EMA, 16 and 10 December 2010*
(www.ema.europa.eu).

Carbapenem

Summary report on adverse drug reactions

Malaysia. The National Pharmaceutical Control Bureau issued a summary report of carbapenems and ADRs in the Malaysian Adverse Drug Reactions Newsletter of August 2010. There have been 248 ADR reports since 2001: 150 reports (256 events) for imipenem; 62 reports (105 events) for meropenem; 36 reports (49 events) for ertapenem. The majority of the ADRs reported are from the following system organ class (SOC): skin and appendages; central and peripheral nervous system; liver and biliary system; gastro-intestinal system; psychiatric; and general disorders. The Newsletter says that central nervous system side effects such as myoclonic activity, confusional side effects and seizures as well as skin reactions such as rash, pruritus, urticaria, Stevens-Johnson syndrome (rare) and toxic epidermal necrolysis (rare) are documented in the local product package inserts.

According to the summary report, 39 ADR reports of seizures have been received in association with imipenem. The reports involved paediatric and elderly patients. Of the patients who experienced seizures during imipenem therapy, 15 (38.4%) had decreased renal function. The National Pharmaceutical Control Bureau advises that imipenem is excreted mainly by the kidneys, and therefore, individualization of the dose of imipenem should be considered for the elderly and patients with impaired renal function in order to reduce the possibility of seizure activity. There are 18 ADR reports of psychiatric effects received related to ertapenem therapy. Confusion,

hallucination and delirium were reported. The National Pharmaceutical Control Bureau states that patients with central nervous system disorder will have increased risk to these adverse effects, and therefore, dose adjustment of ertapenem or use of other alternatives should be considered. Other common ADRs reported include: general disorders (fever, chills, rigors), gastro-intestinal system disorders (diarrhoea, nausea, vomiting) and liver and biliary system disorders (ALT increased, hepatic enzymes increased, jaundice cholestatic, liver function tests abnormal NOS)

Reference:

Malaysian Adverse Drug Reactions Newsletter, August 2010, National Pharmaceutical Control Bureau, Ministry of Health, Malaysia (www.bpfk.gov.my)

Clozapine

Risk of life-threatening gastrointestinal hypomotility

Canada. Health Canada alerted health-care professionals to the potential for life-threatening gastrointestinal hypomotility associated with the use of clozapine. Gastrointestinal hypomotility may be aggravated by combining clozapine with other potentially constipating medications. Clozapine is an atypical antipsychotic agent that is indicated in the management of treatment-resistant schizophrenia. Constipation is a common adverse reaction to the medicine. The Canadian product monograph lists paralytic ileus as a contraindication to clozapine use. The monograph says that clozapine has potent anticholinergic effects that have

been associated with varying degrees of impairment of intestinal peristalsis, from constipation to intestinal obstruction, faecal impaction and paralytic ileus. On rare occasions, these cases have been fatal. According to Health Canada, clozapine's anticholinergic and antiserotonergic effects may contribute to gastrointestinal hypomotility and colonic distension. Intraluminal distension in turn can compromise capillary circulation and lead to colonic mucosal ischemia. In addition, severe faecal retention resulting from hypomotility may promote colonic distension, accumulation of gas and fluids, and bacterial proliferation in the affected bowel segment. Bacteria may then invade the underlying ischemic mucosa, resulting in necrosis and systemic sepsis. Health Canada also warns that the potential for complications and death from severe gastrointestinal hypomotility is considerable. Late presentation and diagnosis of bowel obstruction may contribute to fatal outcomes in patients using clozapine.

As of 15 July 2010, Health Canada received 704 reports of gastrointestinal adverse reactions suspected of being associated with the use of clozapine. Of these, 28 deaths involving people with adverse reactions related to intestinal obstruction were identified. Six cases were considered difficult to assess because the reports contained limited or conflicting clinical information. Of the remaining 22 cases, 13 involved men and nine involved women. The median age of patients was 61 years. A prior history of constipation was noted in six reports. Thirteen reports involved the use of other medications with the potential

to cause or aggravate constipation.

Examples included other antipsychotic agents (e.g., methotrimeprazine, loxapine and olanzapine), medications used to manage drug-induced extrapyramidal symptoms (e.g., benzotropine and procyclidine) and medications indicated for the treatment of urinary tract disorders (e.g., oxybutynin and tolterodine). Use of a laxative before the intestinal obstruction developed was reported in four cases. The total daily dose of clozapine, which was reported in 17 cases, varied from less than 300 mg (five cases) to more than 600 mg (two cases). The median daily dose in the remaining 10 cases was 550 mg. Time to onset of adverse reactions ranged from about two weeks to many years. In three cases, death was related to aspiration pneumonia associated with ileus.

Health Canada advises that patients taking clozapine should be monitored for the development of constipation. Symptoms of serious gastrointestinal complications may be nonspecific and may include abdominal pain or distension, vomiting, constipation, change in bowel habit and fever. Whenever possible, concomitant use of other medications with the potential to cause or aggravate constipation, particularly those with anticholinergic properties, should be avoided.

(See Newsletter No.6, 2007 for warning on gastrointestinal effects of clozapine in New Zealand.)

Reference:

Canadian Adverse Reaction Newsletter, Health Canada, Volume 21, Issue 1, January 2011 (www.hc-sc.gc.ca).

Codeine

Advice against codeine use in breastfeeding

New Zealand. The New Zealand Medicines and Medical Devices Safety Authority (Medsafe) reminded health-care professionals that codeine use by breastfeeding mothers has been associated with fatal cases of infant morphine toxicity. The labels for over-the-counter (OTC) products containing codeine have been updated to advise against codeine use in breastfeeding except on medical advice. The doses of codeine available in some OTC preparations are considered sufficient to cause morphine toxicity in breastfed infants. Medsafe states that patients should be advised of the symptoms of morphine toxicity in themselves (nausea, vomiting, somnolence, constipation and/or difficulty caring for the baby) and their baby (increased sleepiness, difficulty breastfeeding, breathing difficulties or limpness). Patients should also be advised to discontinue codeine and to seek medical attention immediately if these symptoms occur.

(See WHO Pharmaceuticals Newsletter No.5&6, 2008 for warning on risk of morphine-related symptoms in breastfed babies in Canada.)

Reference:

Prescriber Update Vol. 31, No.4 December 2010, (www.medsafe.govt.nz).

Non-steroidal anti-inflammatory drugs

Reducing the risk of gastrointestinal reactions with NSAIDs and/or COX-2 inhibitors

New Zealand. The Medsafe advised on the risk of gastrointestinal (GI) reactions with non-steroidal anti-inflammatory drugs (NSAIDs). The Medsafe says that an analysis of reports sent to the Centre for Adverse Reactions (CARM) shows most patients experiencing GI adverse reactions with NSAIDs or COX-2 inhibitors had other risk factors for these events. Risk factors include: age greater than 65 years; history of peptic ulcer or GI bleeding; previous gastric irritation with NSAID use; use of multiple NSAIDs or COX-2 inhibitors; and concomitant use of corticosteroids, anticoagulants and SSRIs. Prescribers are advised that for all patients requiring treatment with either a non-selective NSAID or COX-2 inhibitor, the extent and severity of GI events can be reduced by:

- using the lowest effective dose for the shortest duration possible;
- avoiding the concomitant use of more than one NSAID, or a NSAID with a COX-2 inhibitor;
- avoiding the concomitant use of aspirin and/or an anticoagulant where possible. If such a combination is necessary, a gastro-protective agent such as a proton pump inhibitor should be considered;
- identifying patients with risk factors for serious GI adverse events and considering the use of a gastro-protective agent such as a proton pump inhibitor.

Reference:

*Prescriber Update Vol. 31, No.4
December 2010,
(www.medsafe.govt.nz).*

Somatropin**Ongoing review of somatropin and possible increased risk of death**

Europe (1). The EMA has announced that the CHMP has started a review of the safety of somatropin-containing medicines authorised centrally or by national procedures in the European Union (EU). The CHMP will look into all available data on somatropin to reassess the benefit-risk balance of these medicines. Somatropin is a human growth hormone that is manufactured using recombinant DNA technology. Somatropin is used to treat a number of conditions associated with a lack of growth hormone and short stature, including children who fail to grow due to a lack of growth hormone, Turner syndrome or chronic renal insufficiency.

The EMA explains that the review was initiated further to information received from the French medicines agency on a long-term epidemiological study called Santé Adulte GH Enfant (SAGhE), in patients treated during childhood for idiopathic lack of growth hormone and idiopathic or gestational short stature with somatropin-containing medicines. The study results suggest an increased risk of mortality with somatropin therapy compared with the general population. The study is still ongoing. The EMA advises prescribers to strictly follow the indications and the approved doses. The maximum recommended dose of 50µg/kg weight/day for somatropin-containing

medicines should not be exceeded.

USA (2). The US FDA issued a Drug Safety Communication informing the public of the results of the Santé Adulte GH Enfant study in France (see item above). In the United States, recombinant human growth hormone is used in the pediatric population to treat short stature due to growth hormone deficiency (including idiopathic growth hormone deficiency), Turner syndrome, Noonan syndrome, Prader-Willi syndrome, short stature homeobox-containing gene (SHOX) deficiency, chronic renal insufficiency, idiopathic short stature and children small for gestational age.

The review of this potential risk is ongoing. The US FDA states that at this time, it believes the benefits of recombinant growth hormone continue to outweigh its potential risks. The Agency recommends that patients continue their recombinant human growth hormone treatment as prescribed by their healthcare provider.

References:

(1) *Press release, EMA,
16 December 2010
(www.ema.europa.eu).*

(2) *FDA Drug Safety
Communication, US FDA,
22 December 2010
(www.fda.gov).*

Egypt. The Egyptian Pharmacovigilance Center issued several safety warnings, including the following, in its eleventh periodic newsletter in December 2010.

- On 3 June 2010, the Central Administration of Pharmaceutical Affairs (CAPA) decided to add a warning to the insert leaflet of simvastatin (cholesterol-lowering medicine) containing products about possible drug interactions with amiodarone, verapamil, or diltiazem, in association with the increased risk of myopathy/rhabdomyolysis.
- On 21 October 2010, the CAPA decided to withdraw the marketing authorization of all products under registration containing dextropropoxyphene (opioid painkiller).
- A new boxed warning will be added to the insert leaflet of trastuzumab (Herceptin) (anti-cancer drug) stating that exposure to trastuzumab during pregnancy can result in oligohydramnios, and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death.

Reference:

*The Egyptian Pharmacovigilance
Center Newsletter 11,
Volume 1, December 2010*

Inspection of Manufacturing Sites for Active Pharmaceutical Ingredients within the WHO Prequalification of Medicines Programme

Background

The WHO Prequalification of Medicines Programme (PQP) aims to make quality medicines available for the benefit of those in need of WHO priority medicines. This is achieved through evaluation of product dossiers, inspection of manufacturing sites and clinical research organizations (CRO), and by building national capacity for sustainable manufacturing and monitoring of quality medicines.

When the product dossier and all relevant manufacturing and clinical sites have been found acceptable, the product is prequalified and listed on the WHO Prequalification Programme website, together with the applicant's name and the corresponding manufacturing site of the finished product.

<http://apps.who.int/prequal/query/ProductRegistry.aspx?list=all&contentType=prequalifiedProduct>

General information

PQP embraces the concept that *"good quality must be built in the product during its design and manufacturing process; it cannot be tested into the product afterwards"*.

Chris Joneckis, Ph.D., senior adviser for chemistry, manufacturing and controls (CMC) issues, noted that *"quality, safety and effectiveness must be designed and built into the product. Quality cannot be inspected or tested into the finished product."*

<http://www.entrepreneur.com/tradejournals/article/154459079.html>

One of the important components of a pharmaceutical product is the active pharmaceutical ingredient (API). Ensuring the quality of the API greatly contributes to achieving the objective of building the quality, safety and efficacy into the product. One of the strategies employed by the PQP to achieve this is through inspection of API manufacturing sites to assess compliance with Good Manufacturing Practices (GMP), and to verify data submitted in product dossiers.

'Expressions of Interest' (EOI) invites manufacturers to submit a request for an evaluation of their product(s). The current 'Expressions of Interest', published on the web site at www.who.int/prequal (go to Prequalification of APIs) and http://apps.who.int/prequal/info_applicants/info_for_applicants_EOIs.htm includes products containing the following APIs (Table 1):

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| HA - ARVs | HA - OPs | AM | TB | RH | IN | Zn |
|---------------|------------------|------------------------------|------------------|----------------------|-------------|--------------|
| Abacavir | Acyclovir | Amodiaquine, | Amikacin | Desogestrel | Oseltamivir | Zinc sulfate |
| Atazanavir | Amitriptyline | Artemether | Capreomycin | Estradiol cyprionate | Zanamivir | |
| Didanosine | Amphotericin B | Artesunate | Cycloserine | Estradiol valerate | | |
| Efavirenz | Azithromycin | Artesunate | Ethambutol | Ethinylestradiol | | |
| Emtricitabine | Benzylpenicillin | Dihydroarteminin | Ethionamide | Etonogestrel | | |
| Indinavir | Bleomycin | Lumefantrine | Isoniazid | Levonorgestrel | | |
| Lamivudine | Cefixime | Mefloquine | Kanamycin | Magnesium sulphate | | |
| Lopinavir | Ceftriaxone | Piperaquine PO4 [#] | Levofloxacin | MPA [®] | | |
| Nelfinavir | Chlorphenamine | Pyrimethamine | Moxifloxacin | Mifepristone | | |
| Nevirapine | Ciprofloxacin | Sulfadoxine | Ofloxacin | Misoprostol | | |
| Ritonavir | Clarithromycin | | PAS ⁵ | Norethisterone | | |
| Saquinavir | Clindamycin | | Prothionamide | Norgestrel | | |
| Stavudine | Codeine | | Pyrazinamide | Oxytocin | | |
| Tenofovir DF* | Dapsone | | Rifampicin | | | |
| Zidovudine | Etoposide | | Streptomycin | | | |
| | Fluconazole | | Terizidone | | | |
| | Folinic acid | | | | | |
| | Ganciclovir | | | | | |
| | Ibuprofen | | | | | |
| | Itraconazole | | | | | |
| | Loperamide | | | | | |
| | Morphine | | | | | |
| | Pentamidine | | | | | |
| | Pyrimethamine | | | | | |
| | Rifabutin | | | | | |
| | Spectinomycin | | | | | |
| | Sulfadiazine | | | | | |
| | Sulfamethoxazole | | | | | |
| | Trimethoprim | | | | | |
| | Vinblastine | | | | | |
| | Vincristine | | | | | |

Table 1. APIs

Inspections

API manufacturing site inspections were started in 2003. An inspection team normally consists of a WHO inspector based in Geneva and a co-inspector appointed by the WHO from a Pharmaceutical Inspection Cooperation Scheme (PIC/S) member inspectorate. An inspector (or inspectors) from the National Drug Regulatory Authority of the country, in which the manufacturing site is located is invited to participate as an observer.

Risk management principles are used to select the site to be inspected, the duration of the inspection and the frequency of inspection. In terms of priorities, inspection of sites for Finished Pharmaceutical Products (FPP) comes first followed by sites for APIs, CROs and Quality Control Laboratories (QCL) in that order. The table below (Table 2) shows some examples of relative risks associated with products.

| PRODUCT TYPE / ACTIVITY | RELATIVE RISK CATEGORY | | | |
|--|------------------------|------|--------|-----|
| | CRITICAL | HIGH | MEDIUM | LOW |
| Finished Products: | | | | |
| Sterile finished products | √ | | | |
| Non-sterile finished products | | √ | | |
| APIs: | | | | |
| Sterile APIs | | √ | | |
| Non-sterile APIs where there is a special risk (e.g. isomerism, polymorphism, special risk of harmful impurities, etc) | | | √ | |
| Other non-sterile APIs | | | | √ |
| QC Laboratories | | | √ | |
| CROs | | | √ | |

Table 2. Relative Risk categories

More specifically, for APIs, additional risk factors are considered. These parameters include:

- Polymorphism
- Solubility in water
- Complexity of the route of synthesis
- Solvents used
- Impurities
- Sterile versus non sterile API
- Fermentation
- Toxicity
- Activity/potency
- Particle size
- Other properties identified to be considered
- Site compliance information e.g. from previous inspections (WHO/EDQM/Other)
- Type and number of FPPs in which the API is used

The following order is provided for guidance in determining priorities:

- Sterile APIs
- Re-inspection when it is more than 12 months past the re-inspection due date
- A new API manufacturer, when the product prequalification process may be held up by lack of GMP evidence for the API manufacturer
- The sole supplier of an API
- The API is produced by fermentation
- The API is used in paediatric PQ medicines
- The API is used in a number of PQ products

All manufacturers of APIs used in prequalified medicinal products should comply with GMP. As a default, all manufacturers of APIs used in prequalified medicinal products should be inspected by the PQP. An inspection by the PQP may be omitted when other acceptable evidence of GMP compliance is provided by the API manufacturer. An inspection by another acceptable organization, such as the EDQM (European Directorate for Quality of Medicines), a PIC/S member country, or the US FDA, may be considered in lieu of an on-site WHO PQP inspection, when:

- The inspection was conducted within the last 2 years with a positive compliance outcome, and
- The scope of the inspection covered the specific API in question, and
- The API manufacturer submits a copy of the last inspection report for review by the PQP. The review must determine that the inspection was comprehensive and that the inspection report supports the final outcome.
- Irrespective of the above, the PQP reserves the right to inspect any API manufacturer if considered necessary on a risk basis.

Whether inspected by the PQP or GMP compliance is based on an inspection by another acceptable organization, on-going GMP compliance must be confirmed at least every 4 years.

Norms and Standards Used

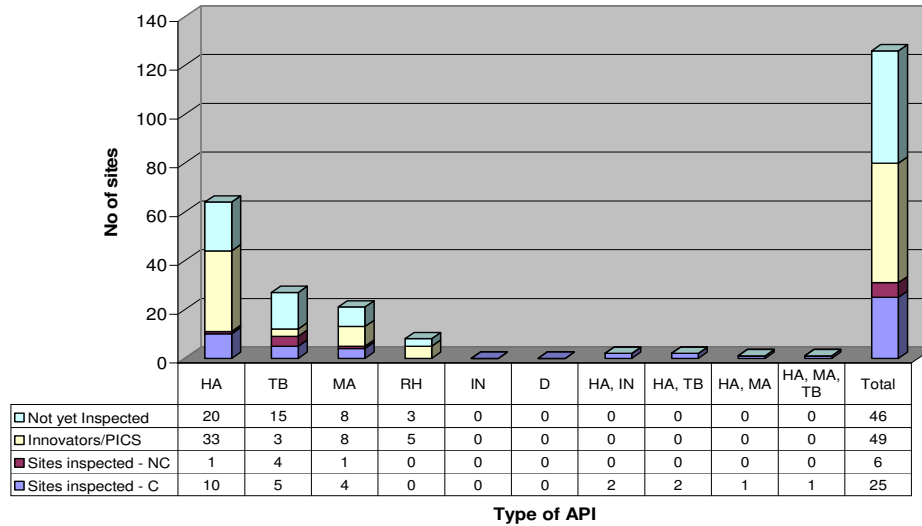
The WHO norms and standards are used in the inspection of API sites. The WHO Expert Committee on Specifications for Pharmaceutical Preparations revised the WHO GMP for APIs, and accepted a new text that is the same as the principles of *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients* (ICH Q7, published by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH). As a result a new *WHO good manufacturing practices for active pharmaceutical ingredient*, (WHO TRS, 2010, No. 957, Annex 2): was published in 2010. http://whqlibdoc.who.int/trs/WHO_TRS_957_eng.pdf#page=144

Statistics

Out of 126 API sites participating in PQ activities, 49 were accepted based on approval by PICS inspectorates and/or ICH countries, while 31 were inspected by WHO inspectors. Six of the inspected sites were found to operate at an unacceptable level of compliance with WHO GMP.

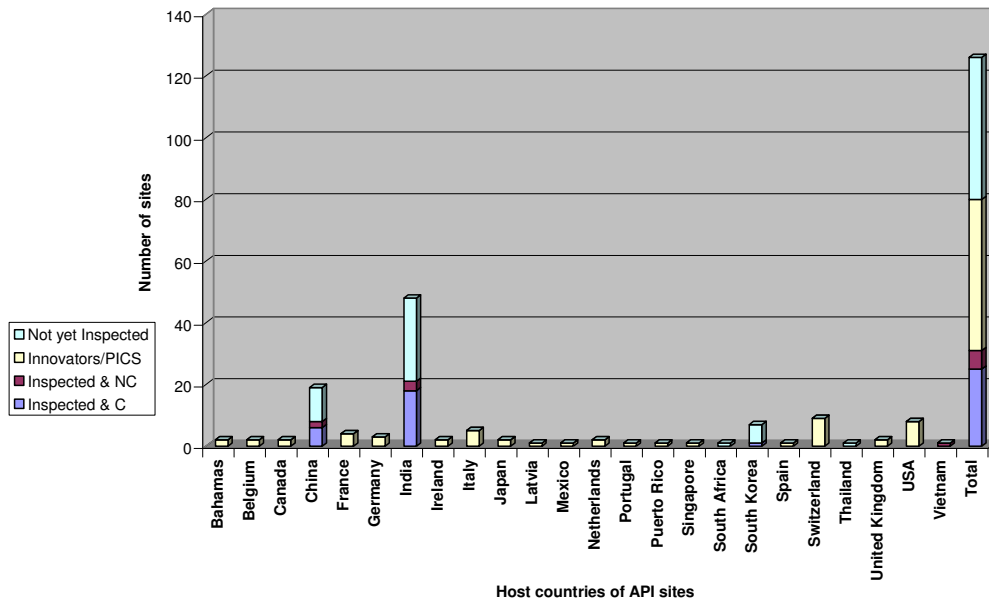
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INSPECTION STATUS OF API SITES USED IN PRODUCTS UNDER WHO PREQUALIFICATION



Most of the API sites were located in India and China and that is where most of the inspections have taken place.

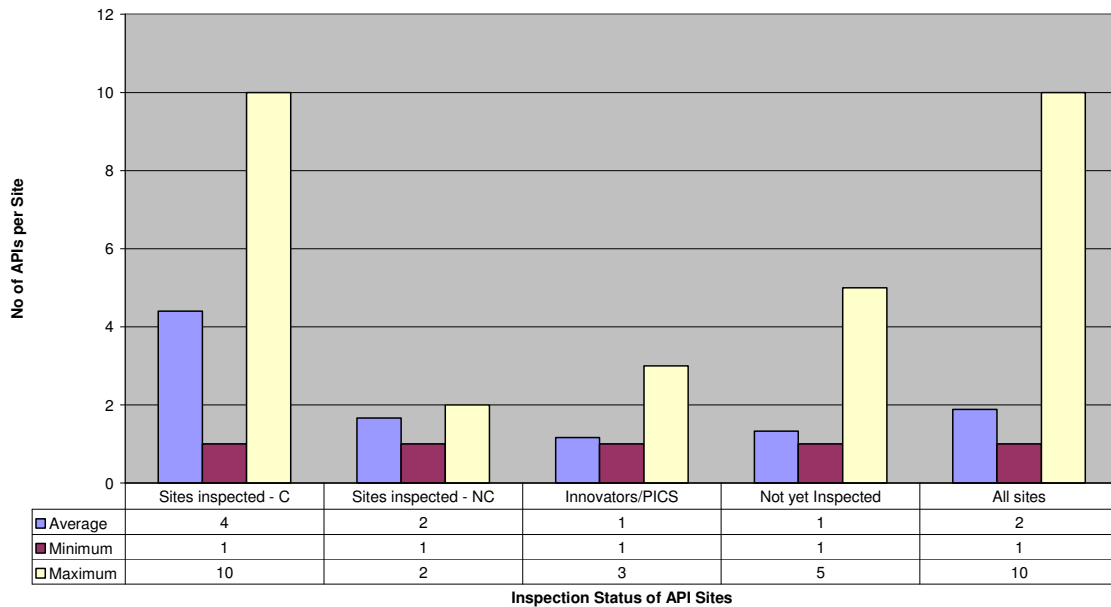
Host Countries for API Sites within the WHO Prequalification of Medicines Programme



The sites inspected are those producing many APIs (average four APIs per site) mainly for HIV/AIDS, TB and MA in that order.

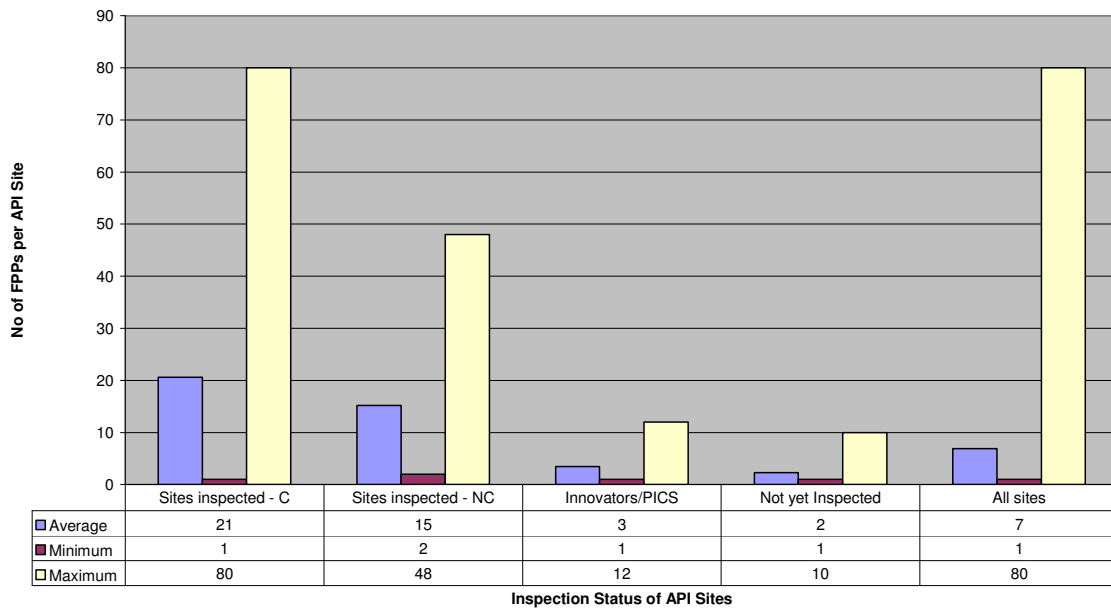
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APIs PER SITE



The sites inspected were the ones producing APIs used in most FPPs (average each API site representing 21 FPPs). This demonstrates maximizing use of available inspection resources.

NUMBER OF FPPs USING APIs FROM EACH SITE

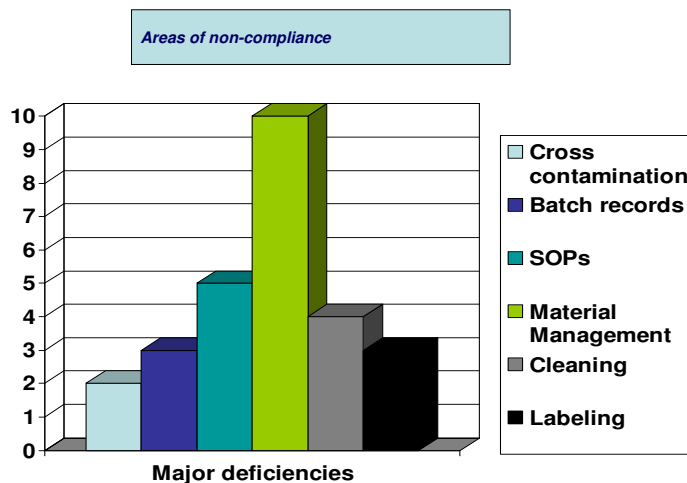


According to the WHO PQ quality assurance system and procedure for prequalification, API sites should be re-inspected on regular basis. Usually the interval between inspections is two to three years.

Key Observations of API inspections

Deficiencies observed during inspections of API sites have been mainly in materials management, documentation, cleaning and cross-contamination.

Inspection of API manufacturers



Meeting of the Global Advisory Committee on Vaccine Safety (GACVS)

8 - 9 December 2010

At its meeting of 8-9 December 2010, GACVS considered the following issues: the safety of MenAfriVac, the meningococcal A conjugate vaccine introduced in West Africa in December 2010; the risk of intussusception following rotavirus vaccination; the safety of pandemic influenza vaccines; and the safety of yellow fever vaccines for HIV-positive individuals.

Safety of the meningitis A conjugate vaccine

Following review of the data for the meningococcal A conjugate vaccine, MenAfriVac, collected in Burkina Faso, Mali and Niger in September 2010, GACVS concluded that there appeared to be no outstanding safety issues related to its use. As the vaccine is currently administered in campaign settings and had not been clinically evaluated among pregnant women, the question of restricting the vaccination of women in this group was considered by the Committee. Consideration was also given to the risk-benefit of providing the vaccine to lactating women.

Given the clear benefits of the vaccine, the increased risk of disease in the geographical area, past experience using similar vaccines in comparable conditions, and the lack of alternative ways of protecting pregnant women from epidemic meningitis, GACVS supported WHO's technical guidance that MenAfriVac should be offered to pregnant and lactating women residing in the meningitis belt during any stage of pregnancy or lactation. However, GACVS emphasized the need for additional post-marketing surveillance to provide more complete information about the safety profile of the vaccine, including its effects in specific groups, especially pregnant women.

Rotavirus vaccines and intussusception

In view of the association of a previously-marketed rotavirus vaccine (Rotashield) with an increased incidence of intussusception (an uncommon form of bowel obstruction), GACVS reviews all post-marketing studies of the currently-available vaccines, Rotarix and RotaTeq, to have considered a potential link between the vaccines and an increased rate of intussusception. Data from Australia, Brazil, Mexico and the U.S.A were reviewed at the December meeting. Post-marketing surveillance suggests a possible increased risk of intussusception shortly after the first dose of rotavirus vaccine in some populations. If confirmed, the level of risk observed in these studies is substantially lower than 1 case/5 000 - 10 000 infants who received the Rotashield vaccine. The benefit of rotavirus vaccination in preventing rotavirus gastroenteritis and its consequences is substantial. Additional data are being collected and analysed, and will be reviewed by GACVS when available.

Safety of pandemic influenza A (H1N1) 2009 vaccines

GACVS reviewed data on the safety of pandemic influenza A (H1N1) 2009 influenza vaccines. Overall, safety information continues to be reassuring. Since the Committee's earlier report in June 2010, data from passive surveillance from different countries has not generated any new safety concerns other than reports of narcolepsy from Finland and Sweden in August. These reports are being investigated by independent groups in Europe. Final analyses of active surveillance studies are anticipated to be completed by late 2011.