

WHO PHARMACEUTICALS NEWSLETTER

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

The aim of this Newsletter is to disseminate information on the safety and efficacy of pharmaceutical products, based on information 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:

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News & Issues

This is the first issue for the year 2005. The cover page is green, representing, we like to think, the need for fresh ideas and out-of-the-box thinking in pharmacovigilance. Inside you will find the usual format, with items on safety of medicines and their regulation. We welcome additional comments on how we could make this publication more valuable.

Two training programmes/workshops in pharmacovigilance have already been held this year, one in India, as part of the launch of the new system for promoting Indian Pharmacovigilance (details on page 8) and one in Spain, the workshop on 'New Challenges in Clinical Safety, Pharmacovigilance and Vaccine Vigilance' by the International Society of Pharmacovigilance, ISOP. The WHO Collaborating Centre, in Uppsala, will conduct its training course on Pharmacovigilance in May.

Selective Serotonin Reuptake Inhibitors (SSRIs) are again in the news, this time for potential neonatal withdrawal effects in children following SSRI exposure, *in utero*. Using this as a case-in-evidence (see section on Drugs of Current Interest) we appeal, yet again, to all Member States to step-up reporting to the WHO global database for adverse drug reactions.

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AMIODARONE

Medication Guide to be dispensed along with medicine

USA. Wyeth Pharmaceuticals Inc., under advice from the United States Food and Drug Administration (US FDA), is directing health professionals to distribute a medication guide to all patients while dispensing amiodarone (Cordarone) tablets to those patients. Amiodarone, an antiarrhythmic drug, is associated with substantial toxicity and is, therefore, indicated only in patients with life-threatening arrhythmias. The medication guide highlights some of the serious and potentially fatal side-effects that may result from the use of amiodarone and provides general information to the patient about amiodarone, conditions when amiodarone may not be taken, relevant medical history that a patient needs to share with the physician before starting the medication, etc. However, this guide is not to be used as a substitute for talking to patients about the risks relative to benefits associated with taking amiodarone tablets.

Reference:

'Dear Health-care Professional' letter from Wyeth Pharmaceuticals Inc., 30 December 2004. Available on the Internet at www.fda.gov

ATOMOXETINE

Labelling to include liver injury warning

USA. The US FDA has issued a Talk Paper advising of changes to the US atomoxetine (Strattera) labelling, following two reports of severe liver injury in patients who had received the agent for several months. Atomoxetine is a selective norepinephrine reuptake inhibitor indicated in the treatment of attention deficit hyperactive disorder (ADHD) in children, adolescents and adults. The atomoxetine

labelling is to be updated to include a bolded warning regarding the risk of severe liver injury that could progress to liver failure, requiring liver transplantation or resulting in death, although it is noted that the actual number of cases is unknown. The new warning advises discontinuation of atomoxetine if patients develop jaundice or laboratory evidence of liver injury. Eli Lilly has agreed to issue a 'Dear Health-care Professional' letter regarding these changes, and will update the atomoxetine patient package insert to include information about the signs and symptoms of liver disorders.

Reference:

FDA Talk Paper, 17 December 2004. Available on the Internet at www.fda.gov

BENZATHINE BENZYL-PENICILLIN/PROCAINE BENZYL-PENICILLIN

Label changes highlight appropriate use

USA. King Pharmaceuticals Inc., has issued a 'Dear Health-care Professional' letter advising of changes to the US labelling of benzathine benzylpenicillin/procaïne benzylpenicillin (Bicillin C-R) and benzathine benzylpenicillin (Bicillin L-A) that highlight appropriate use and administration of these products. The letter advises that benzathine benzylpenicillin (Bicillin L-A) is the only approved benzylpenicillin indicated for the treatment of venereal disorders, including syphilis, in the USA. However, King Pharmaceuticals has been made aware of post-marketing reports of benzathine benzylpenicillin/procaïne benzylpenicillin (Bicillin C-R) being used to treat patients with syphilis; they warn that use of

Bicillin C-R instead of Bicillin L-A may result in inadequate treatment. To reflect this important difference, the cartons and syringe labels of the two agents have been modified. In addition, a boxed warning has been added to the labelling of both Bicillin C-R and Bicillin L-A to emphasize that these products are not intended for IV use, which has been associated with heart arrest and death.

Reference:

'Dear Health-care Professional' letter from King Pharmaceuticals Inc., November 2004. Available on the Internet at www.fda.gov

MEFLOQUINE

Patient Information Leaflet to help recognize adverse symptoms

Canada. Hoffman-La Roche is introducing an updated Patient Information Leaflet in every box of mefloquine (Lariam), used in the prophylactic treatment of malaria. The updated leaflet

- is intended to help patients recognize symptoms, including the sudden onset of unexplained anxiety, depression, restlessness, irritability, confusion, a persistently abnormal heart-beat, or palpitations, that may precede rare but potentially serious psychiatric, neurologic, or cardiac adverse events;
- advises patients who develop these symptoms to contact a health-care professional to assess the need for discontinuation of Lariam® (mefloquine) treatment and,
- includes a wallet card containing a summary of the most essential information, that may be cut out and carried by the patient during travel to areas with malaria.

Reference:

'Dear Health-care Professional' letter from Hoffman-La Roche, 24 January 2005. Available on the Internet at www.hc-sc.gc.ca

PARACETAMOL- DEXTROPROP- OXYPHENE

To be withdrawn due to risk of toxicity in overdose

UK. The UK Medicines and Healthcare products Regulatory Agency (MHRA), under advice from its Committee on Safety of Medicines (CSM), has announced the withdrawal of the paracetamol-dextropropoxyphene combination product (co-proxamol) in the UK. The CSM undertook a recent review of the risks and benefits of co-proxamol and has concluded that the efficacy of co-proxamol is poorly established and that the risk of toxicity in overdose, both accidental and deliberate, is unacceptable.

Co-proxamol contains paracetamol (325 mg) and the weak opioid analgesic dextropropoxyphene (32.5 mg). Each year 300-400 fatalities involving co-proxamol are known to occur in England and Wales following deliberate or accidental overdose. Approximately one-fifth of these deaths are considered to be accidental.

The CSM has announced that, in order to minimize disruption of healthcare provision, co-proxamol will be phased out so that patients currently receiving co-proxamol may be switched to alternative pain management regimes at their next routine medication review. The CSM has issued the following interim prescribing advice, pending withdrawal of co-proxamol:

- Co-proxamol is only indicated in the treatment of mild to moderate pain in adults where first-line analgesics have proved ineffective or are

inappropriate. It should not be used for any acute pain management.

- Co-proxamol therapy should not be initiated in new patients.
- Co-proxamol should not be used in patients aged <18 years.
- Co-proxamol is contraindicated in patients who are alcohol-dependent, who are likely to consume alcohol whilst taking co-proxamol, and in those patients who are suicidal or addiction prone.

Reference:

Letter from the Chairman, UK Committee on Safety of Medicines, 31 January 2005. Available on the Internet at www.mhra.gov.uk

SMALLPOX VACCINE

Label to highlight reports of myopericarditis

USA. A black box warning has been added to the labelling of Wyeth's smallpox vaccine, Dryvax, to highlight reports of acute myopericarditis in healthy adults. Although Wyeth no longer manufactures Dryvax, as the World Health Assembly certified the world free of naturally occurring smallpox in the 1980s, the US Government asked Wyeth to test stored batches of the vaccine, and the black box warning applies to those vaccines which have been repackaged for immediate use by firefighters, medical personnel and other first responders. The black box warning states that "acute myopericarditis has been observed after administration of Dryvax to healthy adults", and also warns of encephalitis, progressive vaccinia and severe vaccinia skin infections following vaccination with the agent. The warning states that immunocompromised persons should not receive the vaccine in non-emergency situations.

Reference:

Smallpox vaccine dried, calf lymph type. Prescribing Information, 15 November 2004. Available on the Internet at www.fda.gov

THIORIDAZINE

Withdrawn due to poor benefit/risk profile

Worldwide. Novartis has announced that it will discontinue all forms of thioridazine (Melleril™) worldwide by 30 June 2005, because the benefit/risk profile of the drug no longer meets current clinical and regulatory expectations. Specifically:

- There is evidence of a connection between QTc prolongation, a known side-effect of thioridazine, and cardiac arrhythmias and sudden death in patients with schizophrenia.
- New, improved antipsychotic treatments are now available.

It is recommended that when discontinuing treatment with thioridazine, a gradual reduction in dosage over several weeks is recommended to prevent recurrence of symptoms. There are no evidence-based specific recommendations on initiating treatment with an alternative antipsychotic or other psychotropic medication, and formal practical guidelines for switching antipsychotic medication are also lacking. However, a substantial body of information has been published in peer-reviewed journals reviewing the techniques commonly employed in clinical practice and the important factors that should be considered. All generic versions of thioridazine are also to be discontinued.

Reference:

News & Updates, 25 January 2005. Available on the Internet at www.druginfozone.nhs.uk

ATAZANAVIR- RITONAVIR

Not to be co-administered with omeprazole

Europe. The European Medicines Agency (EMA) has issued a public statement that warns physicians against the co-administration of atazanavir (Reyataz) combined with ritonavir (RTV) and 40 mg omeprazole, a proton pump inhibitor. This warning is based on the observations from a randomized, open-label, multiple-dose drug interaction study performed in healthy volunteers. The study demonstrated a 76% reduction in atazanavir area under the concentration curve (AUC) and a 78 % reduction in atazanavir trough plasma concentration (C_{min}) when atazanavir / ritonavir (300/100 mg) was co-administered with omeprazole 40 mg. The exact mechanism for this interaction is yet to be determined. In the meantime, physicians are advised not to co-administer atazanavir / ritonavir (300/100 mg) with any dose of omeprazole or with any other proton pump inhibitor to avoid risk of reduction in the atazanavir exposure levels in these patients.

Reference:

EMA Public Statement, EMEA/CHMP/202649/2004, 21 December 2004. Available on the Internet at www.emea.eu.int

CELECOXIB

Increased risk of cardiovascular events

Europe, New Zealand, USA. Pfizer has announced that the US National Cancer Institute Data Safety and Monitoring Board has stopped drug administration in the Adenoma Prevention with Celecoxib (Celebrex; APC) trial, as the risk of major cardiovascular events was significantly higher in patients receiving celecoxib than in patients receiving

placebo. The US FDA and the EMA have issued statements detailing the preliminary results, and have requested the full results for review⁽¹⁻⁴⁾.

In the APC study, 2400 patients received celecoxib 400 mg/day, celecoxib 800 mg/day or placebo, for a mean duration of 33 months. The relative risk (RR) of major fatal or nonfatal cardiovascular events (composite endpoint of cardiovascular death, acute myocardial infarction or stroke) was statistically significantly higher in the celecoxib 400 mg/day group (RR 2.5) and in the celecoxib 800 mg/day group (RR 3.4), compared with the placebo group.

Two other celecoxib trials, the Prevention of Spontaneous Adenoma Polyps (PreSAP) trial and the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT), have also been evaluated⁽⁴⁾. The PreSAP trial has been stopped, based on the results of the APC trial, although an increased risk of cardiovascular events with celecoxib 400 mg/day compared with placebo was not observed⁽³⁾. However, the ADAPT study is still ongoing⁽⁴⁾. The FDA has issued an Alert for Practitioners regarding the possible increased risk of cardiovascular events in patients receiving celecoxib⁽⁴⁾. Physicians are encouraged to inform patients of the evolving information about this risk, and are advised to consider alternatives to celecoxib; when this is not appropriate, the lowest effective celecoxib dose should be used. The New Zealand Medicines Adverse Reactions Committee has issued similar advice with regard to all COX-2 inhibitors, broadly supporting the UK National Institute of Clinical Excellence guidance that was distributed to all New Zealand general practitioners⁽⁵⁾.

References:

1. FDA Statement, 17 December 2004. Available on the Internet at www.fda.gov

2. EMA Statement, EMEA/205831/2004, 17 December 2004. Available on the Internet at www.emea.eu.int
3. EMA Statement, EMEA/212271/2004, 22 December 2004. Available on the Internet at www.emea.eu.int
4. FDA Alert for Practitioners (celecoxib), 17 December 2004. Available on the Internet at www.fda.gov
5. Medsafe Media Release, 21 December 2004. Available on the Internet at www.medsafe.govt.nz

DARBEOETIN ALFA

Adverse outcomes associated with off-label dosing strategies

USA. The US FDA and Amgen notified health-care professionals of revisions to the WARNINGS and PRECAUTIONS sections of the prescribing information for darbepoetin alfa (Aranesp), indicated for the treatment of chemotherapy-induced anaemia in patients with non-myeloid malignancies. This safety information alerts physicians to the adverse effects observed with other products in this class in association with off-label dosing strategies. Two recent investigational studies with other erythropoietic products permitted or required dosing to achieve haemoglobin levels of greater than 12 grams per decilitre. An increased frequency of adverse patient outcomes, including increased mortality and thrombotic vascular events were reported in these studies. As indicated in the darbepoetin alfa (Aranesp) prescribing information, the target haemoglobin level should not exceed 12 grams per decilitre in men or women.

Reference:

- 'Dear Health-care Professional' letter, 11 January 2005. Available on the Internet at www.fda.gov

GALANTAMINE

Ineffective and possibly unsafe in mild cognitive impairment

Canada. Janssen-Ortho Inc., under advice from Health Canada, is warning health professionals that according to preliminary data from two investigational studies, galantamine (Reminyl), a cholinesterase inhibitor, does not appear to be effective in treating patients with mild cognitive impairment (MCI). In addition, the initial analysis of both studies showed that 15 patients died in the galantamine (Reminyl) treatment group and five in the placebo treated group. The causes of death were mainly cardiovascular or cerebrovascular in nature. Janssen-Ortho is reminding that galantamine (Reminyl) is approved only for the symptomatic treatment of patients with mild to moderate dementia of the Alzheimer's type and that it is not to be used outside of its approved indication.

Reference:

'Dear Health-care Professional' letter from Janssen-Ortho Inc., 21 January 2005. Available on the Internet at www.hc-sc.gc.ca

GLUCOSAMINE

Concerns about hypercholesterolaemic effects

Denmark. The Danish Medicines Agency has sent out a 'rapid alert' notification to all European regulatory agencies, including the EMEA, requesting any information about a potential cholesterol-raising effect of the nutritional supplement, glucosamine. The product is marketed for some forms of osteoarthritis and in several countries, including Denmark, is registered as a medicinal product. This move follows an article in the Danish journal that reported increased

cholesterol levels in three patients, possibly as a result of glucosamine use. There are 67 side-effect reports associated with glucosamine use in the Danish Medicines Agency database, most of which are described in the product summary. However, there are also reports of suspected adverse effects that are not identified in the product summary, including increased INR (n = 3), vision disorders (3), peripheral oedemas (3), dyspnoea (2), pulmonary embolism (1), seizures (1), myocardial infarction (1), increased liver enzymes (1), an increased serum creatinine level (1), and an increased cholesterol level (1). The agency advises that the Swedish authorities have also received two reports of hypercholesterolaemia. The companies marketing glucosamine are invited to join the Danish Medicines Agency in addressing the problem, by submitting the statutory safety updates.

References:

1. *Scrip World Pharmaceutical News No 3000, 29 October 2004.*
2. *Stenver DI. Possible interaction between glucosamine and cholesterol. Reply. Ugeskrift for Laeger 25, No. 44, October 2004. (Danish; summarized from a translation.)*

NAPROXEN

Long-term study indicates cardiovascular risk

USA. The US FDA is alerting healthcare providers to emerging information from a long-term prevention trial, the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT), that the risk of cardiovascular and cerebrovascular events may increase among patients taking naproxen, a non-steroidal anti-inflammatory drug (NSAID). The US FDA will be analysing all available information from

these studies to determine whether additional regulatory action is needed. In the meantime, prescribers are cautioned:

- to carefully weigh the benefits and risks in patients currently on naproxen therapy,
- to always prescribe within the recommended dose of 250-500 mg twice a day and,
- to advise patients to adhere to the recommended daily dose indicated in over-the-counter naproxen preparations.

Several of the cyclooxygenase-2 (enzyme) specific inhibitor drugs (rofecoxib, celecoxib etc.) are currently under investigation for a full understanding of their adverse cardiovascular effects (see WHO Pharmaceuticals Newsletter No. 5, 2004 and section under 'Celecoxib' in this issue). Naproxen, a non-selective over-the-counter NSAID, is also being investigated to determine appropriate regulatory action. The US FDA is planning an advisory committee meeting in February 2005 to discuss the issues surrounding these drugs.

Reference:

FDA Alert for Health-care Providers (Naproxen), 23 December 2004. Available on the Internet at www.fda.gov

NEVIRAPINE

Not recommended in women with CD4+ cell counts greater than 250 cells/mm³

USA. The US FDA issued a public health advisory to inform health-care providers and patients about recent safety-related changes to the nevirapine (Viramune) label and about appropriate use of HIV triple combination therapy containing nevirapine, a treatment option in the United States which is increasingly

being used globally. The Indications and Usage section now recommends against starting nevirapine treatment in women with CD4+ cell counts greater than 250 cells/mm³ unless benefits clearly outweigh risks. This recommendation is based on a higher observed risk of serious liver toxicity in patients with higher CD4+ cell counts prior to initiation of therapy. Females have a 3-fold higher risk of symptomatic liver toxicity than males, and females with CD4+ cell counts > 250 cells/mm³ have a 12-fold higher risk of symptomatic liver toxicity than females with CD4+ cell counts < 250 cells/mm³. In addition, the revised label now includes a Medication Guide to inform patients about risks associated with nevirapine when used for the treatment of HIV.

Reference:

FDA Public Health Advisory for Nevirapine, 20 January 2005. Available on the Internet at www.fda.gov

PROPOFOL

Adverse events with both low- and high-rate infusions

Australia. The Australian Adverse Drug Reactions Advisory Committee (ADRAC) has received a report of torsade de pointes and a report of lactic acidosis associated with propofol (Diprivan; Recofol) infusions at rates of 100 mg/h and 30 mg/h respectively, over approximately 24 hours. The ADRAC warns that, although high-rate and prolonged propofol infusions increase the risk of life-threatening propofol infusion syndrome, low-rate infusions for short periods of time may also be associated with serious adverse events.

Reference:

Australian Adverse Drug Reactions Bulletin 23, No. 6, December 2004.

ROSUVASTATIN

More reports of rhabdomyolysis

Canada. Health Canada has issued a warning to the Canadian public that a further six reports of rhabdomyolysis in patients receiving rosuvastatin (Crestor) have been received since a Public Health Advisory was issued in June 2004. The reports are currently under assessment, as is the safety profile of rosuvastatin, particularly the 40 mg dose. Health Canada has also issued an Advisory to warn of the possible association between rosuvastatin and rhabdomyolysis and to remind patients to consult their physician if they have risk factors for developing the condition. Patients who experience "any unexplained muscle pain, muscle weakness or cramps, or any brown or discoloured urine", during treatment with rosuvastatin or any other cholesterol-lowering drug, are advised to contact their physician immediately. Health Canada recommends that all patients receiving rosuvastatin, or any other cholesterol-lowering drug, "should be using the lowest dose that will meet their treatment goal".

Reference:

Health Canada Media Release, 29 November 2004. Available on the Internet at www.hc-sc.gc.ca

Reports in WHO-file:

Rhabdomyolysis 13

Selective Serotonin Reuptake Inhibitors (SSRIs): Potential Adverse Effects in Neonates

'Why reporting matters'

SSRIs are, arguably, one of the most written about classes of medicines, both for putting back quality into the lives of thousands of patients battling with serotonin-dependent depression and for their reported suicidal effects in adolescents. The latest write-up on the SSRIs is the Lancet article 'Selective serotonin reuptake inhibitors in pregnant women and neonatal withdrawal syndrome: a database analysis' by Emilio J Sanz, Carlos De-Las-Cuevas, Anne Kiuru, Andrew Bate and Ralph Edwards (Lancet 2005, 365: 482-87). Using the WHO global database for adverse drug reaction reports, the authors have investigated whether use of SSRIs in pregnant women might cause neonatal withdrawal syndrome. They conclude that 'SSRIs, especially paroxetine, should be avoided or cautiously managed in the treatment of pregnant women with a psychiatric disorder'.

One of the most important tasks of the WHO Programme for International Drug Monitoring is to identify 'signals' of drug safety problems as early as possible. Spontaneously reported cases of suspected adverse drug reactions (ADRs) are forwarded from national pharmacovigilance centres (appointed by national governments) in 75 countries (plus 13 associated

countries) to the WHO Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre (*the Centre*), in Sweden. The case reports, recorded in a common format, are processed and stored in the ADR database. Over 3.1 million case records are maintained by *the Centre*, which provides a unique source of international ADR information. Although the WHO ADR data are not homogeneous with respect to origin or the probability that the pharmaceutical product caused the adverse reaction, they have a proven use in the early detection of signals. A signal is defined by WHO as 'reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously'.

Since 1998 *the Centre* has been using the Bayesian Confidence Propagation Neural Network (BCPNN) methodology to identify unexpectedly strong statistical associations between drugs and adverse reactions. The BCPNN uses a logarithmic measure of disproportionality called the information component (IC) for the calculation of 'observed to expected' reporting ratios. Using this methodology, the complete WHO database is screened quarterly generating a computerized table known as the combinations database containing more than 2000 new associations that stand out statistically from the background of all reports in the database. It is sent every quarter to the national pharmacovigilance centres (National Centres, NCs) who review its international contents for issues of relevance to their own countries. At *the Centre*, associations are checked against available product information literature. For drugs where the reaction is not found or not described well enough, case reports are retrieved from the WHO database. *The Centre*

then sends the cases to the most appropriate expert in *the Centre's* global review panel to assess the evidence for the reaction being related to the suspected drug using their clinical experience and pharmacological knowledge.

The additional 'signal' detection work by *the Centre* and its review team is complementary to the work performed by national pharmacovigilance centres and not a substitute for local evaluation and decision-making.

An association between paroxetine and neonatal convulsions was identified already in December 2001 by *the Centre* by the above process and NCs were notified. In August 2003 the Australian Therapeutic Goods Administration (TGA) drew attention to this reported problem in its Adverse Drug Reactions Bulletin. In 2004 both the US FDA and Health Canada issued warnings about the potentials of *in utero* SSRI-exposure. The current 2005 Lancet paper analyses further data, accumulated up to 2003 in the WHO database, using 102 cases (reported from 11 countries) of neonatal effects associated with SSRI use and confirms these warnings. Again, as with the cyclooxygenase-2 inhibitor story (see WHO Pharmaceuticals Newsletter No.5, 2004), the WHO database helped identify, well ahead of time, the drug and the adverse effects requiring special attention. However, this is not just about reminding Member States of what the International Drug Monitoring Programme can do. Rather, it is an opportunity to reinforce that a facility exists and that it should be put to optimal use with more active collaboration from the Member States.

That the WHO database is the largest source of global information on adverse reaction reports cannot be contested. Neither can we challenge the

fact that spontaneous reports form a valuable component of the 'early warning system'. The Centre encourages regular reporting, but less than ten countries send reports once per month; some countries do not send any reports at all; some countries send reports in large batches and nothing in between for long periods. This attitude needs to change in order to improve the database both qualitatively and quantitatively, to make it truly current, representative and global, and to make the early warning system work in real terms. It is all about preventing avoidable harm and regular reporting will contribute.

References:

1. *EJ Sanz et al., Lancet, 365:482-487, 2005.*
2. *Australian Adverse Drug Reactions Bulletin, Vol. 22, no.4, August 2003.*
3. *Reactions Weekly (Adis International), No.7, 26 June 2004.*

The Indian Pharmacovigilance Programme: a curtain raiser

India is a country with a population of 1.6 billion. It has 18 official languages and 35 States and Union Territories. It is the fourth largest producer of pharmaceuticals in the world. It is therefore an enormous challenge to establish and maintain a credible adverse drug reaction monitoring programme in the country. However, the central drugs regulatory authority - Central Drugs Standard Control Organization (CDSCO) - has done just that.

The national Pharmacovigilance Programme was launched in November 2004. The Programme aims to foster a culture of adverse drug event reporting in its first year of operation and subsequently aims to:

- generate broad-based adverse drug reactions (ADR) data on the Indian population and share this information globally through the WHO Programme for International Drug Monitoring;
- ensure optimum safety of medicinal products in the Indian market;
- provide technical expertise for evaluating adverse events (AE) reports from clinical trials in India.

Although India started participating in the WHO Programme for International Drug Monitoring in 1998, it was not until 3 years later that CDSCO started to hold discussions with the various players - health professionals, pharmacists, the pharmaceutical industry, clinical research organizations and academics from related fields - in order to plan a nation-wide pharmacovigilance programme. These discussions eventually culminated in the protocol for pharmacovigilance in India.

The national pharmacovigilance programme consists of:

- two zonal centres situated in Mumbai and New Delhi;
- five regional centres situated in Kolkata, Mumbai, Nagpur, New Delhi and Pondicherry;
- a yet to be defined number of peripheral centres.

It is envisaged that the peripheral centres will collect their data and send them on to the regional centre which in turn will submit the data to the zonal centre where it will be consolidated, analysed and forwarded to the national Pharmacovigilance Advisory Committee which makes appropriate recommendations to CDSCO for regulatory interventions. The information collected at the regional centres and the zonal centres will also be submitted to the WHO global database.

The first training course involving most of the zonal, regional and peripheral centres was held in Mumbai in January 2005. There were 28 participants in total who varied from community pharmacists in small peripheral centres to clinical pharmacologists in large teaching hospitals. The course was organized by Dr Urmila Thatte and her staff from the Nair Medical Hospital, Mumbai. It was funded by WHO/SEARO. The course material was adapted from the course provided by the WHO Collaborating Centre for International Drug Monitoring in Uppsala. Mr Sten Olsson from Uppsala was the main facilitator with assistance from Dr Mary Couper, WHO. Other facilitators were from India making presentations ranging from drug development to traditional medicine and to ethical issues for the programme to consider. Dr Kris Weerasuriya, Regional Adviser (PSM, SEARO) made a presentation at the course in which he indicated that WHO/SEARO would continue to support the programme provided that results were tangible in the form of a significant number of reports being sent to the global database in Uppsala by June.

The enthusiasm and dedication that was evident throughout the course needs to be sustained in order for this ambitious programme to be effective. This can only succeed if all the centres work effectively together.