

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 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:

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News & Issues

In early February, WHO met in Lusaka with five African countries in a follow-up meeting to a workshop conducted in 2003 in Zambia to assess progress and barriers in implementing pharmacovigilance activities for the safety monitoring of artemisinin combination products in the malaria programmes in these countries. A pharmacovigilance training course was organized from 12 to 23 February in Morocco. The course was offered in French, to help launch a national pharmacovigilance programme in 13 countries in Francophone Africa. The WHO Advisory Committee on Safety of Medicinal Products will meet from 26 to 27 February, to discuss current issues and concerns in pharmacovigilance. We will bring you a summary of all these events in the next issue of the newsletter.

In capturing adverse reactions to medicines, national pharmacovigilance centres design a reporting form that best meets the centre's needs. Would a 'generic reporting form' help harmonize efforts and improve the quality of data captured? Indeed, is it even possible to design such a generic adverse reaction reporting form? What are the constraints we are likely to face in designing such a generic form? Sten Olsson, WHO Collaborating Centre for International Drug Monitoring, Sweden discusses some of these issues in his article (page 7).

In the next issue, we hope to introduce a Letters section. Here we will include, if appropriate, various comments from our readers, either on specific items in the newsletter or on other issues of medicine safety. We hope that this will allow even better interaction with our readers. We invite you to send your letters with comments to pals@who.int. But we caution that we may not be able to publish every letter.

We hope that you will find useful the usual sections on Regulatory Matters and Safety of Medicines.

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Aprotinin injection

Use limited to patients at increased risk of blood loss during heart surgery

USA. The safety warnings have been strengthened and the approved use limited to specific situations for aprotinin injection (Trasylol), a product used before heart surgery to reduce bleeding and the need for blood transfusions. The label now specifies that aprotinin (Trasylol) should only be given to patients who are at an increased risk of blood loss and blood transfusion in the setting of coronary bypass graft surgery, when patients undergo cardiopulmonary bypass. The label also has the new warning that aprotinin increases the possible risk for kidney damage. These measures follow a United States Food and Drug Administration (US FDA) conducted safety review triggered by the results of two published research studies: one study reported an increase in the possibility of kidney damage, heart attack and stroke in patients treated with aprotinin compared to those treated with other drugs, while the second study showed only an increase in the possibility of kidney damage compared to other drugs. The Agency has also received the results of an additional safety study from Bayer, (Marketing Authorization Holder for Trasylol) that suggest, in addition to serious kidney damage, an increased risk of death, congestive heart failure and strokes with the product. According to the US FDA, these results are being reviewed and may result in other actions, including additional changes to the labelling.

Reference:

FDA News. U.S. Food and Drug Administration, 15 December 2006 (www.fda.gov).

Buflomedil Higher dose tablets withdrawn due to risk of suicide

France. Agence française de sécurité sanitaire des produits de santé (Afssaps) has decided to withdraw buflomedil 300 mg tablets from the market and to strengthen the summary of product characteristics (SPC) for buflomedil 150 mg. The agency undertook a benefit-risk evaluation of buflomedil (used chiefly to treat peripheral vascular disease), following the results of two enquiries about cardiovascular and neurological toxicity in accidental or voluntary buflomedil overdoses. The agency says that neurological and serious cardiac adverse events occurred within 15–90 minutes in cases of suicide with buflomedil and, because of a narrow therapeutic index, the clinical manifestations of buflomedil overdose are serious. The overdose cases are difficult to manage and often have fatal outcomes, adds the agency; the majority of voluntary overdose cases occurred with 300 mg dose of buflomedil. According to Afssaps, the toxic dose of 3 g can easily be reached with buflomedil 300 mg tablets; therefore, the benefit-risk for buflomedil 300 mg is considered negative. The agency has decided to recall batches of buflomedil 300 mg tablets from the market, and to include the following information in the SPC for buflomedil 150 mg:

- indicated for improvement of symptoms of peripheral occlusive arterial disorders or Raynaud's disease only;
- contraindicated in patients with severe renal failure (creatinine clearance <30 mL/min);
- dose adaptation in patients with moderate renal failure (creatinine clearance between 30 and 90 mL/min)

- and low body weight (<50 kg);
- control of creatinine clearance before and during treatment; and
- information about low therapeutic range of buflomedil.

(Reports in the WHO database: Neurologic disorder - 1 report from 1999)

Reference:

Reactions 1131: 2, 9 December 2006.

Heparin Delayed onset of heparin-induced thrombocytopenia

USA. The US FDA has informed health-care professionals that Baxter has revised the warnings section of the labelling for heparin sodium injection to highlight the potential of delayed onset of heparin-induced thrombocytopenia (HIT), and to highlight that HIT may develop into heparin-induced thrombocytopenia and thrombosis (HITT). Furthermore, the Agency states that thrombotic events could be the initial presentation of HITT, which can happen up to several weeks after heparin discontinuation, and that patients should be evaluated for HIT and HITT if they present with thrombocytopenia or thrombosis after heparin discontinuation.

Reference:

MedWatch Internet posting, 8 December 2006 (www.fda.gov).

Methadone Risk of QT prolongation and Torsades de pointes

France. Afssaps, the Regulatory Agency in France, has issued a letter of information to health professionals and care-givers working with patients of drug

abuse. Methadone is used in the treatment of opioid dependence and for analgesia in moderate to severe pain. The letter warns about the evidence of QT-prolongation and torsades de pointes associated with the use of methadone. The Agency advises that these adverse effects were usually observed in patients at risk of QT prolongation or in those receiving a high dose of methadone (>120 mg/day). The Summary of Product Characteristics for methadone has been revised with this information. ECG monitoring is recommended in patients with risk factors for QT prolongation including:

- history of QT-prolongation, congenital or acquired;
- family history of sudden death;
- methadone dose >120 mg/day
- use of other medications known to prolong QT-interval, induce hypokalaemia, bradycardia, or inhibit the metabolism of methadone.

The interactions and contraindications sections of the SPC for methadone have been modified with details of medicines to be avoided as concomitant treatment, needing special clinical and ECG monitoring or favouring methadone dose reduction. The full list can be accessed from Afssaps home page on the internet (www.afssaps.sante.fr).

(Also see WHO Pharmaceuticals Newsletter, No. 5, 2005, for previous information from New Zealand).

Reports in WHO database: Arrhythmia - 32 (since 1986)

Reference:

Lettre d'information aux medicines prescripteurs, cardiologues, pharmaciens et acteurs de soins auprès de patients usagers de drogue. Afssaps, 2 January 2007 (www.afssaps.sante.fr).

Quinine

Consumers cautioned against off-label use in treating leg cramps

USA. The US FDA is cautioning consumers against off-label use of quinine in leg cramps, citing serious safety concerns, including deaths, associated with quinine products. Quinine is used in treating malaria. Only one quinine product (Qualaquin) is approved by the US FDA in treating certain types of malaria without complications. However, the Agency notes that there are multiple unapproved products containing quinine in the US market and has ordered the responsible firms to stop marketing these. Quinine is a drug with a narrow therapeutic window, with a small margin between effective and toxic doses. But the Agency advises that because malaria is life-threatening, the risks associated with quinine use are justified for that condition; but it should not be used to treat or prevent leg cramps. Quinine drugs are associated with serious side effects such as cardiac arrhythmias, thrombocytopenia and severe hypersensitivity reactions. There is also the potential for serious interactions with other drugs. The US FDA notes that since 1969 it has received 665 reports of adverse events with serious outcomes associated with quinine use, including 93 deaths.

Reference:

FDA News. U.S. Food and Drug Administration, 11 December 2006 (www.fda.gov).

Rituximab

Fatal PML following off-label use in systemic lupus erythematosus (SLE)

Switzerland, USA. Roche Pharma, in collaboration with

Swissmedic, the Swiss regulatory agency (1) and the US FDA (2) are informing health-care professionals of two fatal cases of progressive multifocal leukoencephalopathy (PML), a viral infection of the central nervous system in patients treated with rituximab (Rituxan, Genentech, US; MabThera, Roche Pharma, Switzerland). These two patients received rituximab for the treatment of systemic lupus erythematosus (SLE). SLE is not an approved indication for rituximab; rituximab is approved only in the treatment of patients with non-Hodgkins lymphoma and in patients with rheumatoid arthritis whose disease no longer responds to other common treatments and works by blocking the effect of specific immune cells in the blood known as B cells for up to six to nine months. PML appears to be a risk in patients treated with rituximab for any reason. There have been 23 confirmed cases of PML in patients with lymphomas who received rituximab. The majority of these patients had also received other drugs known to affect the immune system. Physicians and patients are advised to be aware of the risk of PML in patients treated with rituximab. Patients who experience signs of PML such as major changes in vision, balance or coordination, or who experience confusion should promptly contact their physician. The product label is being updated with this information on PML.

(Post-marketing reports of bowel obstruction and gastrointestinal perforation had led to a previous revision of the rituximab product label. See WHO Pharmaceuticals Newsletter No. 6, 2006)

References:

1. *Lettre au médecin. Roche Pharma (Schweiz), le 24 janvier 2007 (www.swissmedic.ch)*
2. *FDA News. U.S. Food and Drug Administration,*

18 December 2006
(www.fda.gov)

Sodium phosphate oral solution

Electrolyte and renal function disturbances in the elderly

France. Ferring and Casen Fleet Laboratories, in consultation with Afssaps, have revised the product monograph for sodium phosphates oral solution (Fleet® Phospho-Soda®), advising prior evaluation of risk factors and caution when using the product in the elderly. Sodium phosphates oral solution is used as a purgative as part of a bowel cleansing regimen in preparing patients for surgery or for preparing the colon for X-ray or endoscopic examination. The product has been associated with rare but severe and potentially fatal cases of electrolyte disturbances in the elderly. Gastroenterologists and nephrologists are reminded to pay special attention while using the product in special populations including the elderly, individuals with asymptomatic renal insufficiency, patients with a history of acute myocardial infarction or unstable angina, etc. Very rare cases of nephrocalcinosis (deposits of calcium phosphate tubules in the kidney) leading to acute or chronic renal insufficiency have also been associated with use of this product, particularly in elderly patients who were on anti-hypertensives or other medications (e.g. diuretics or other products known to cause dehydration). When considering the use of sodium phosphates oral solution in patients at risk, it is important to evaluate the baseline electrolyte levels before and after administration and to ensure sufficient fluid replacement to prevent dehydration and serious electrolyte problems.

Reference:

Lettre destinée aux gastro-entérologues et néphrologues ville et hospitaliers. Laboratoire Casen Fleet et Laboratoire Ferring SAS France, 13 décembre 2006
(www.afssaps.sante.fr).

Topical anaesthetic creams

Pharmacies warned to cease compounding standardized versions

USA. The US FDA is warning five pharmacies to cease compounding and distributing standardized versions of topical anaesthetic creams, which are marketed for general distribution rather than responding to the special requirements of individual patients. Such creams contain high doses of local anaesthetics including lidocaine, benzocaine, prilocaine and tetracaine. The Agency warns that exposure to high concentrations of local anaesthetics can lead to reactions such as irregular heartbeats and seizures. According to the FDA, two deaths have been linked to anaesthetic creams compounded by two of the five pharmacies receiving warning letters. The Agency says their warning serves as a general warning to firms that produce standardized versions of anaesthetics.

Reference:

FDA News. U.S. Food and Drug Administration, 5 December 2006
(www.fda.gov).

Cough and cold medications Deaths in infants reviewed

USA. According to a recent report, during 2004 - 2005, an estimated 1 519 children aged less than two years were treated in the Emergency Departments in the United States for adverse events, including overdoses, associated with cough and cold medications. The Centers for Disease Control and Prevention (CDC) and the National Association of Medication Examiners (NAME) have determined cold and cough medications to be the underlying cause of three deaths (infants aged ≤ 6 months) in 2005; all three infants had high levels of pseudoephedrine (a nasal decongestant) in postmortem blood samples. One infant had received both a prescription and an over-the-counter cough and cold combination medication at the same time. The dosages at which cough and cold medications cause illness or death in children aged < 2 years are not known. Nor do approved dosing recommendations exist for prescribing cough and cold medications for this age group. The US FDA advises that because of the risks of toxicity, absence of dosing recommendations, and limited published evidence of effectiveness of these medications in children < 2 years, parents and other care givers should not administer cough and cold medications to this population without first consulting the health-care provider and should follow the provider's instructions precisely. Furthermore, clinicians are advised to use caution when prescribing cough and cold medications to children aged < 2 years; clinicians should ask care givers about other over-the-counter

medications that may have been given to these children, to avoid overdose from multiple medications that contain the same ingredient. Besides these recommendations, public health officials have taken additional safety measures including

- an enforcement action to stop the manufacture of unapproved carbinoxamine-containing medications that were inappropriately labelled for use in children despite safety concerns associated with the use of carbinoxamine in children aged < 2 years;
- an act that banned over-the-counter sale of cold medications that contain pseudoephedrine etc (although this act was enforced to inhibit access to pseudoephedrine, and thus the manufacture of methamphetamine);
- replacing pseudoephedrine with other nasal decongestants in many of the cough and cold preparations.

Reference:
Morbidity and Mortality Weekly Report, 12 January 2007, 56(01): 1-4
(www.cdc.gov/mmwr).

3,4 diamino-pyridine (DAP) Not for treating fatigue in multiple sclerosis patients

France. Based on its evaluation of the benefit-risk profile of 3,4 diaminopyridine, Afssaps, the Regulatory Agency in France is advising health professionals that there is no evidence of the efficacy of 3,4 diaminopyridine in treating fatigue associated with multiple sclerosis (MS). This combined with the insufficient preclinical data give DAP a poor benefit-risk profile. DAP is therefore not to be used in treating fatigue in MS patients. Physicians who do prescribe DAP for the above use will be responsible for their decision. However, DAP has a favourable benefit-risk profile in treating the associated

symptoms of Lambert-Eaton myasthenic syndrome in those patients with no other treatment alternatives.

Reference:
Letter to health-care professionals (in French). Afssaps, 11 December 2006
(www.afssaps.sante.fr).

Gefitinib No survival advantage; increased risk of tumour haemorrhage

Canada. AstraZeneca Canada has issued a 'Dear Health-care Professional' letter highlighting Health Canada-endorsed safety information regarding the lack of survival benefit and an increased incidence of tumour haemorrhage associated with the use of gefitinib (Iressa) in patients with squamous cell cancer of the head and neck. The letter describes the top-line results from a trial that examined the efficacy and safety/tolerability of gefitinib (Iressa) 250 mg and 500 mg versus methotrexate in a refractory unselected population of 486 patients with recurrent squamous cell carcinoma of the head and neck (SCHNN). In summary, the results suggest:

- a potential new toxicity finding of tumour haemorrhage in gefitinib (Iressa) recipients: tumour haemorrhage occurred in 8.9% and 11.4% of gefitinib (Iressa) 250 mg and 500 mg recipients, respectively, versus 1.9% of methotrexate-treated patients;
- a lack of survival advantage for gefitinib (Iressa) 250 mg and 500 mg compared with methotrexate: the median overall survival time was 5.6 and 6.0 months for gefitinib (Iressa) 250 mg and 500 mg, respectively, versus 6.7 months for methotrexate.

AstraZeneca says that patients with head and neck cancer treated with gefitinib (Iressa) should be informed of these results by their physician and alternative treatment options

should be discussed where appropriate. Furthermore, the company is conducting a comprehensive review of the above trial to further understand the significance of these results.

Reference:

'Dear Health-care Professional' letter from AstraZeneca Canada Inc., 1 December 2006 (www.hc-sc.gc.ca).

Leflunomide Reports of interstitial lung disease

Australia. The Australian Adverse Drug Reactions Advisory Committee (ADRAC) has so far received 669 reports associated with leflunomide use and, of these, 142 reports involve respiratory symptoms. Leflunomide is used to treat the symptoms of rheumatoid arthritis. One or more of the following reactions were described in 22 reports: lung infiltration (n = 4), pulmonary fibrosis (3), interstitial lung disease (ILD) (9) or pneumonitis (8). According to ADRAC, although the medical terms differ, it is likely that all of these 22 reports were in fact reporting ILD. Among the 22 reports of ILD possibly associated with leflunomide, 16 females and six males were affected (age range 52 to 84 years). Four patients died. Although leflunomide was administered concomitantly with methotrexate in the majority of reports (16 out of 22), in six of these reports methotrexate had been used long-term without problems. In the six reports in which methotrexate was not used, leflunomide was the only medicine suspected of causing the interstitial lung disease. Eight patients (of the 22) required ICU admission for intubation and ventilatory support. The time to onset ranged from two weeks to 25 months but the majority of the cases had an onset of three to five months following the

commencement of leflunomide. ADRAC advises that the pulmonary status of patients should be evaluated before leflunomide initiation, and that patients should be monitored closely during treatment; leflunomide discontinuation should be considered if worsening or new onset pulmonary symptoms develop.

Reports in WHO database:

Pulmonary infiltration - 17 (since 2000)
Pulmonary fibrosis - 25 (since 2000)
Pneumonitis - 52 (since 2000)

Reference:

Australian Adverse Drug Reactions Bulletin, December 2006, 25(6): 22-23 (www.tga.gov.au).

Tramadol Withdrawal reactions may be a bigger problem than previously thought

Sweden. The Swedish adverse reactions database, SWEDIS, contains 71 reports from 1996 to 2005 of abstinence/withdrawal symptoms with tramadol, 25 of which are also classified as dependence, habituation or increased tolerance. The treatment duration in the 71 reports ranged from one week to more than three years, at dosages of 50–2000 mg, indicating that withdrawal symptoms have been reported at low-to-normal doses and after treatment periods of <6 months. Some of the symptoms that were reported following tramadol withdrawal were similar to that observed with opioids, including nausea, pain, shivering, sleep disorders and sweating while other atypical symptoms such as anxiety, hallucinations, muscle cramps, nervousness, paraesthesia and tremor have also been reported. According to the Swedish Medical Products Agency some of these reports may convey a risk for dependency and abuse with tramadol, and even short-term

use may lead to troublesome withdrawal symptoms in the absence of a slow phase-out. Physicians are reminded of the potential for withdrawal reactions and/or the risk of dependency with tramadol.

Reports in WHO database:
Withdrawal syndrome - 648 (since 1990)

Reference:

Translated from the Swedish Medical Products Agency Information bulletin, 14 November 2006 (www.lakemedelsverket.se).

Tumour necrosis factor (TNF)- α inhibitors Increased risk of malignancy

Australia. According to ADRAC, tumour necrosis factor (TNF)- α inhibitors may predispose patients to an increased risk of malignancy or accelerate its development. (TNF)- α is a cellular protein produced by the immune system and is an important mediator of many diseases, including inflammatory arthritis and inflammatory bowel disease. Currently, three (TNF)- α blocking agents are registered in Australia: infliximab (Remicade) - for the treatment of Crohn's disease, rheumatoid arthritis and ankylosing spondylitis; etanercept (Enbrel) - for rheumatoid arthritis, polyarticular juvenile chronic arthritis, psoriatic arthritis and ankylosing spondylitis; and adalimumab (Humira) - for rheumatoid arthritis. Since 2000, ADRAC has received 319 reports involving (TNF)- α inhibitors. The more serious reports were as follows: malignant melanoma (3 reports), tuberculosis (4), lymphoma (5), anaphylaxis (9), sepsis (10), lupus or lupus-like syndrome (22) and pneumonia/lower respiratory tract infections (23). The

Australian Product Information advises caution when considering (TNF)- α blocking therapy in patients with a history of malignancy, or when considering continued treatment in those who develop a malignancy.

Reference:

Australian Adverse Drug Reactions Bulletin, December 2006, 25(6): 22-23 (www.tga.gov.au).

Medicines Evaluation Board (MEB) and the Netherlands Healthcare Inspectorate sign agreement with the US FDA

On 2 October 2006 a confidentiality agreement was signed between the Dutch competent authorities and the U.S. Food and Drug Administration. This agreement will allow exchange of confidential information between the competent authorities in the two countries. This exchange of information may have important benefits for the protection and advancement of public health.

Reference: www.cbg-meb.nl.

The need for a generic form for spontaneous reporting of drug related problems

Sten Olsson, WHO Collaborating Centre for International Drug Monitoring

Background

The WHO-QSM unit has recently received requests for a general WHO form to be used for spontaneous reporting of suspected adverse drug reactions (ADRs). The demand has come from Public Health Programmes getting involved in the establishment of pharmacovigilance systems for new medicines in many countries around the world.

Current situation

There is currently only one internationally recognized reporting form for submission of ADR case information to national pharmacovigilance centres, the so called CIOMS-I form. It was developed in 1990 to allow marketing authorization holders (MAH) to submit ADR information to regulators using one and the same format in all countries. The form was not designed for soliciting case information from health professionals and would most probably not work for that purpose.

The WHO reporting form, developed in 1968 and revised in 1981 for submission of case information from national pharmacovigilance centres to the WHO database, is international in scope but is not useful for collecting original data from health professionals. Since 2001 it is no longer accepted as a paper form within the WHO Programme, but only as a format for electronic submissions.

Also the ICH-E2b format provides a standard for exchange of case information electronically between the Marketing Authorization Holder (MAH) and regulators on an international scale. The E2b format is very extensive and cannot be translated into a single-sheet reporting form.

Although all pharmacovigilance centres developed after the 1960s have had access to model reporting forms from established centres, they have all chosen to develop and use their own version. The book 'National Pharmacovigilance Systems' (Sten Olsson ed, 2nd edition 1999) contains an overview of the content of 40 reporting forms in use up until the end of the 1990s. It demonstrates a great variation in the data items asked for. Only 11 data elements were common to all forms and 20 elements occurred in a majority of forms (Appendix 1). In total, 65 different data items were represented on the 40 forms. Presently 98 countries are associated with the WHO Programme for International Drug Monitoring. They have all developed their own reporting forms.

Basic considerations

There are two main aspects of an ADR reporting form that are related but have to be considered separately:

- Content
- Design

The content of the reporting form has to do with the data items being requested about the case. The design refers to the arrangement of tick boxes, fields to be filled in, the use of colours, logos etc.

Discussion

The form, whether paper-based or electronic, provided to health professionals and/or patients for collection of case details about suspected drug related diseases is a critical document, forming the basis for subsequent efforts in the creation of new knowledge. No specific guidelines exist on how a good form should be composed and designed. How to optimize the efficiency of the key document in the data collection process has been the subject of very little attention or systematic research.

Benefits of a generic reporting form

It would seem attractive to have a common, internationally accepted form for ADR reporting that could be put to immediate use in the field whenever a system for spontaneous reporting is introduced in a country or in a treatment programme. There would be less need for local pharmacovigilance competence in developing the form and the barrier for getting started might be lower. The generic reporting form

would give guidance as to what data items are important to collect. If the form was adopted by WHO and carried the WHO logo, it would be associated with status and credibility. The use of the same form for data collection in many countries and in different settings would facilitate uniformity of data. The data elements of the form could be made to comply with, and be a subset of, the E2b format. It would then be easy to transcribe data from such a form to an E2b compatible database.

Reservations about having a generic reporting form

The aim and focus of spontaneous reporting systems are different depending on the local situation. The variability could be due to different reasons.:

- *The type of data requested* e.g. adverse reactions, lack of efficacy, quality defects, poisoning, dependence, medication errors. Countries have different aims with their reporting programmes and are organized differently. Quality defects and ADRs might not be dealt with by the same authority. There might be a separate system for reporting poisoning for example. A generic form encompassing all possible needs might not be effective in meeting the local needs
- *The intended target group for reporting* e.g. community health-workers, pharmacists, traditional healers, patients or physicians. The reporting form has to be adapted to the intended reporters. The same wording does not appeal equally to physicians and patients. Since countries choose different target groups for their reporting system a generic reporting form might not be well designed for any of their target groups.
- *Each treatment programme would have a need for specific information not requested by others* e.g.:
 - CD-4 count and viral load in HIV/AIDS
 - diagnostic accuracy of disease in malaria and other parasitic infections
 - batch numbers, programmatic errors, strain specificity, cold-chain information in immunization programmes.

It would be difficult to accommodate the needs of all the various programmes unless there is sufficient space for free text. However, with that solution there is a risk that the reporter would miss some of the key data elements.

The process of developing a reporting form is educational. We have to discuss the importance of requesting the various data items and weigh it against the feasibility of capturing the information. A generic reporting form might request information that is unavailable or completely irrelevant in the local situation. If a local decision has been made to include a certain data element in the form, it is easier justifying the importance of that element to a local reporter

To be effective a reporting form needs to be available in the local language and have features relating to the responsible authority e.g. a logo, the address and contact details of the issuing institution. There might need to be a reference to a legal reporting requirement. A common WHO form provided in English would, in very few instances, be useful in its original form. It would need to be translated and adapted. This seriously reduces the benefit of having a generic WHO reporting form.

Reporting forms should be tested in a local community before the general launch to find out what design solution works best in that community. It is not without reason that there are >100 different reporting forms taken together in the countries (some have more than one) currently operating systems for spontaneous adverse reaction reporting. It would have been easier for the newcomers in the field to adopt a form being used in another country but they have all chosen to design their own.

We are totally dependant on the psychology of the various potential reporters and we have to adapt to the needs of the professionals or patients whom we want to encourage to report. If we start from the perspective of what is most convenient for the management of the pharmacovigilance programme, we are bound to fail.

Conclusion and proposal

A generic WHO form for spontaneous reporting of drug-related problems is not likely to be effective in any particular situation. WHO should however develop a set of guiding principles for the drafting and design of good forms for any setting, covering all the options, including minimum data needed for follow-up and other variables. The principles should apply to any setting, in any language. WHO should also gather the best of the existing forms from a handful of different settings, improve and refine them, and offer them as models of best practice, which can then be modified and adapted for particular situations

Note: The above discussion refers to forms for spontaneous reporting. Forms for use in active surveillance, e.g. cohort-event monitoring, have been suggested by WHO in the relevant context. However, general guidelines on how to design a good form would probably apply to them too.

Appendix I

Overview of national reporting forms

Total number of reporting forms reviewed = 40

Data items occurring on all reporting forms (n = 39 or 40)

Patient data

Identity of patient (name, initials or civil registration number)

Sex

Age or date of birth

Exposure data

Name of suspected drug

Name of concomitant medication

Dosage schedule

Date of first administration

Date of drug withdrawal

Indication for drug treatment

Reaction data

Description of reaction

Date of onset

Additional items occurring on >75% of reporting forms (n = 31 - 38)

Patient data

Patient's medical history

Exposure data

Route of administration

Other observations

Patient outcome

Additional information - free text

Additional items occurring on >50% of reporting forms (n = 21- 30)

Patient data

Weight

Reaction data

Duration of reaction

Other observations

Treatment of reaction

Effect of rechallenge

Administrative

Origin of report