

# Reporting adverse drug reactions

A guide for healthcare professionals

May 2006



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# Editorial board

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## Declaration of interest

There were no competing interests with anyone involved in the research and writing of this report. For further information about the editorial secretariat or board members please contact the Science and Education Department which holds a record of all declarations of interest: [info.science@bma.org.uk](mailto:info.science@bma.org.uk)

# Abbreviations

ADR	Adverse drug reaction
BNF	British National Formulary
CHM	Commission on Human Medicines
CPD	Continuing professional development
DMRC	Defective Medicines Report Centre
DSRU	Drug Safety Research Unit
EMA	European Medicines Agency
GPRD	General Practice Research Database
MHRA	Medicines and Healthcare products Regulatory Agency
MORE	Manufacturer Online Reporting Environment
OTC	Over-the-counter
PEM	Prescription-event monitoring
RMC	Regional monitoring centre
SABRE	Serious adverse blood reactions and events reporting system
SHOT	Serious Hazards of Transfusion

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# Foreword

The BMA has long been concerned with the health of the public and believes that effective reporting of adverse drug reactions (ADRs) is an important mechanism for post-marketing surveillance of medicines and is vital for maintaining drug safety. In 1996 the BMA's Board of Science published *Reporting adverse drug reactions – a policy document*<sup>1</sup>, which discussed the different structures in place within the UK for reporting ADRs. The report focused on the Yellow Card Scheme through which suspected ADRs can be reported spontaneously, but also briefly discussed prescription-event monitoring as a means through which ADRs can be recorded. Since the 1996 BMA report, there have been a number of significant changes to the Yellow Card Scheme. This report includes these changes and acts as a signposting resource for healthcare professionals. Recommendations about ways in which healthcare professionals can help improve reporting of ADRs are listed at the end of this report.

Compared to other countries the number of spontaneous reports submitted in the UK is relatively high and reporting rates in relation to prescription volumes are also among the best in Europe.<sup>2</sup> There are also a number of structured databases which systematically monitor healthcare events, including ADRs, which can be useful tools for pharmacovigilance. Despite this good record, it is vital that healthcare professionals remain vigilant, are aware of the need to report and keep track of any changes to the systems in place. The recent Board of Science report *Over-the-counter medication* (2005)<sup>3</sup> stated that the availability and use of non-prescription drugs that are bought over-the-counter (OTC) have increased in recent years. Increased private sector availability from sources such as newsagents, supermarkets and the internet can result in OTC medications, including herbal remedies, being purchased with little or no support or control from doctors or pharmacists. This trend towards greater self-care can make correct identification of ADRs more difficult if the right questions are not asked of a patient. Problems can also arise if communication breaks down between different healthcare settings. This resource aims to reinforce the importance of pharmacovigilance and the reporting of ADRs in particular.



Professor Sir Charles George  
Chair, Board of Science

The Board of Science, a standing committee of the BMA, provides an interface between the medical profession, the government and the public. The board produces numerous reports containing policies for national action by government and other organisations, with specific recommendations affecting the medical and allied professions.

# Introduction

## What is an adverse drug reaction?

According to information published by the Medicines and Healthcare products Regulatory Agency (MHRA) 'an adverse drug reaction (ADR) is an unwanted or harmful reaction experienced following the administration of a drug or combination of drugs, and is suspected to be related to the drug. The reaction may be a known side effect of the drug or it may be new and previously unrecognised'.<sup>4,a</sup> This is opposed to an adverse event which 'is any undesirable experience that has happened to the patient while taking a drug but may or may not be related to the drug'.<sup>4</sup> In the British National Formulary (BNF) it is noted that an ADR can be caused by any therapeutic agent, including prescribed and OTC drugs, blood products, vaccines, radiographic contrast media and herbal products, and that all of these should be reported.<sup>5</sup>

If an unexpected reaction is observed in a patient it may be difficult to establish its causality and thus if it has resulted from the administration of a drug or combination of drugs. Guidance on factors that should be considered when trying to establish causality of a reaction is provided by the MHRA on their website at [www.mhra.gov.uk](http://www.mhra.gov.uk).<sup>6,b</sup> The resource notes that it is important to consider the nature of the reaction, the timing of the reaction in relation to drug administration, the relationship to the dose administered and other possible causes of the reaction including concomitant medications and the patient's underlying disease. Further information on the different types of ADRs that occur and on identification of ADRs can be found in guidance for healthcare professionals produced jointly by the Department of Health (DH) and the NHS on their PRODIGY guidance website at [www.prodigy.nhs.uk](http://www.prodigy.nhs.uk).<sup>7</sup> For information about allergic reactions to medications, an important type of ADR, refer to the British Society of Allergy and Clinical Immunology which works to improve the management of allergic and related disease, at [www.bsaci.org](http://www.bsaci.org). A clinical review published in the *BMJ* offers a good summary of the importance and types of ADRs that can be experienced.<sup>8</sup>

## The prevalence of ADRs

Adverse reactions are more common than might be expected and there can never be a guarantee that a medicine is completely safe. Determining the precise number of ADRs that are experienced, however, is virtually impossible given the difficulties in assessing causality and the low proportion of ADRs that are reported. ADRs also vary in their severity, by what type of medication they are caused and in what setting they are experienced, making identification complex. Most research which has tried to quantify ADRs has done so by evaluating hospital patients and admissions in particular. A study of hospital admissions in the UK, published in 2004, found that 6.5 per cent of people admitted to hospital had experienced an ADR and that in 80 per cent of those, the ADR was the direct cause of the admission.<sup>9</sup> This research (which excluded admissions due to drug overdose) also found that ADRs accounted for 4 per cent of hospital bed capacity and resulted in a projected annual cost to the NHS of £466 million.<sup>6</sup> The study also found that over 2 per cent of those patients who were admitted to hospital with an ADR died. This would make the overall fatality rate from ADRs within the population 0.15 per cent. Similar results were found

<sup>a</sup>It is important to note that this definition of an ADR according to the MHRA does not exclude overdose or drug misuse. This is opposed to the definition from the WHO, which does exclude overdose and drug misuse from the definition of an ADR.

<sup>b</sup>An alternative guide to identifying ADRs is given in *Clinical medicine* (2005), using the mnemonic TREND, which stands for Temporal relationship, Rechallenge, Exclusion, Novelty, Dechallenge. (Pirmohamed, M (2005) Anticipating, investigating and managing the adverse events of drugs. *Clinical medicine*, 5:1 23-5).

<sup>c</sup>For further information about the economic burden of ADRs see the 2003 report *Adverse events and the National Health Service: an economic perspective, a report to the National Patient Safety Agency* (the Gray report). At [www.npsa.nhs.uk/site/media/documents/940\\_A%20Gray%20final%20report%201103.pdf](http://www.npsa.nhs.uk/site/media/documents/940_A%20Gray%20final%20report%201103.pdf).

by a meta-analysis of ADRs in hospitalised patients in the USA. This study found overall incidence of serious ADRs (on admission and experienced while in hospital) to be 6.7 per cent and of fatal ADRs to be 0.32<sup>10</sup> per cent. Preliminary data from an ongoing contemporary study at the Royal Liverpool University Hospital has indicated that about 16 per cent of patients suffer an ADR as hospital inpatients.<sup>11</sup> Many ADRs are experienced by patients when they are being treated in primary care or as outpatients. It is difficult to quantify the actual prevalence of ADRs and there has been little research into the incidence of ADRs in patients treated in primary care. One small study in the USA found that around 25 per cent of outpatients had experienced an ADR and that in many instances they were preventable or ameliorable.<sup>12</sup> Given the small amount of data, more research should be done into the incidence of ADRs outside secondary care.

### What is pharmacovigilance?

During clinical trials, while there are a number of different test phases (see appendix A),<sup>d</sup> only a small number of patients are exposed to a medication, over a limited period of time, compared to the number that might use it once it is licensed, ie once a marketing authorisation<sup>e</sup> has been granted. Rare adverse reactions, occurring in only a small percentage of cases, after a long period of use or when a drug interacts with a particular combination of other medications or conditions, may not be detected during clinical trials. Pharmacovigilance is the 'science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem.'<sup>13</sup> If ADRs that are not discovered during clinical trials are to be detected, investigated and communicated, and the appropriate action taken, then it is vital that post-marketing pharmacovigilance of all medicines is comprehensive. Effective pharmacovigilance should take into account trends in use, as well as the occurrence of ADRs, enabling more effective advice to be given to those prescribing and using medications and should ensure better standards of safety and efficacy.

There are many different ways in which information can be collected and used for pharmacovigilance. These include the use of data from clinical and epidemiological studies, published medical literature, and information from pharmaceutical companies, morbidity and mortality databases, longitudinal patient databases and spontaneous reporting schemes. This report considers ways in which healthcare practitioners can contribute to the collection of pharmacovigilance data and therefore the focus will be spontaneous reporting of suspected ADRs and longitudinal patient databases.

### Why are pharmacovigilance and reporting ADRs important?

The limitations of clinical trials mean that when a drug is first marketed, much may be known about its efficacy while relatively little may be known about its safety (see box 1).<sup>14</sup> For example, at least 30,000 people need to use a medication in order to identify, with 95 per cent power, an adverse reaction with an incidence of one in 10,000.<sup>8</sup> A relative lack of widespread clinical trials for medicines to treat children means that many drugs are initially only licensed for use in adults, which can leave 'no alternative to the prescriber than to use "off-label" and unauthorised products'<sup>15</sup> in this population. Thus, the need for post-marketing surveillance can be seen as a means to identify drug safety problems not picked up by pre-marketing tests and promulgate any

<sup>d</sup>For further information see the BMA Clinical trials internet resource (2004) at [www.bma.org.uk/ap.nsf/Content/Hubclinicaltrials](http://www.bma.org.uk/ap.nsf/Content/Hubclinicaltrials).

<sup>e</sup>The MHRA operates a system of licensing before the marketing of medicines. Medicines, which meet the standards of safety, quality and efficacy, are granted a marketing authorisation (previously a product licence), which is normally necessary before they can be prescribed or sold. This authorisation covers all the main activities associated with the marketing of a medicinal product.

necessary advice and/or regulatory action to prescribers and users. Pharmacovigilance through, for example, spontaneous ADR reporting or large scale databases, is used to generate hypotheses and signals about potential hazards of marketed drugs that require further investigation. Spontaneous reporting of suspected ADRs is particularly useful in identifying rare or delayed reactions; as such a system enables medicines to be monitored throughout their lifetime. See appendix B for some of the more recent drug safety problems to be identified by the Yellow Card spontaneous ADR reporting scheme.

### Box 1: Limitations of most clinical trials in highlighting a drug's safety

- Homogeneous sample populations.
- Most trials assess relatively healthy patients with only one disease and mostly exclude specific groups such as pregnant women, children and elderly people.
- Sample size.
- Small sample size (up to 1,000 patients) reduces the chance of finding rare adverse effects.
- Limited duration.
- Trials of short duration preclude the discovery of long-term consequences such as cancer.
- Inability to predict the real world.
- Drug interactions can be substantial in a population as patients may take drugs concomitantly, a situation that can almost never be predicted from clinical trials.

Source: Striker B & Psaty B (2004) Detection, verification, and quantification of adverse drug reactions. *BMJ* **329**: 44-7.

In addition to contributing to the safety profiles of existing drugs, pharmacovigilance activities help to improve the knowledge set and contribute to the breadth of epidemiological data. Pharmacovigilance is, therefore, vital for the advancement of future research, medical understanding, drug development and epidemiological studies. Large-scale databases containing longitudinal patient or prescription data reflect routine usage of medications in the general population and provide denominator data which can be used to identify trends.<sup>16</sup>

Any improvements in drug safety or understanding will ultimately lead to improvements in patient care and thus the benefits of effective pharmacovigilance should be appreciated and pursued by all healthcare professionals. Effective spontaneous reporting of suspected ADRs also relies on good communication between healthcare professionals and patients, which in turn should assist good relationships and can improve patient care.

As the Yellow Card Scheme relies on the goodwill of reporters, healthcare professionals should consider it their professional duty to report ADRs. The importance of pharmacovigilance and reporting ADRs is reflected in the General Medical Council's (GMC) core guidance *Good medical practice*, which states that in providing care, doctors have a duty to 'report adverse drug reactions as required under the relevant reporting scheme, and cooperate with requests for information from organisations monitoring the public health'.<sup>17</sup>

# Methods of reporting in the UK

## Spontaneous reporting

The most common way that regulatory bodies collect ADR information for medicines once they are on the market is through voluntary, spontaneous reporting structures. In the UK, the Yellow Card Scheme is run by the MHRA and the Commission on Human Medicines<sup>f</sup> (CHM) and is used to collect information on ADRs from healthcare professionals and members of the public. The original CHM, known as the Committee on Safety of Drugs, was established in 1964 following the thalidomide tragedy<sup>g</sup> and since then, over half a million reports have been collected. Detailed information about the Yellow Card Scheme can be found on the MHRA website at [www.mhra.gov.uk](http://www.mhra.gov.uk).

When the Yellow Card Scheme was first introduced, only doctors and dentists could submit reports. Gradually this has been extended and now all healthcare professionals, including coroners, pharmacists and nurses are able to report ADRs via the scheme. Available data indicate that the introduction of nurse and pharmacist reporting is proving to be very useful.<sup>18,19,20</sup> The extension of reporting to other professionals should not, however, lead to complacency by doctors, who should continue to use the Yellow Card Scheme and take responsibility for reporting suspected ADRs to the regulatory authorities. It is important to appreciate firstly, that the database used by the MHRA can detect duplicate reports. If, therefore, a doctor deems it necessary to submit a Yellow Card they should do so even if there is a possibility that someone else might have done the same. Secondly, different people will include different information when they complete a Yellow Card, all of which is useful in creating a full picture of the reaction that has taken place.

Yellow Cards should be submitted to either the MHRA directly or to one of five regional monitoring centres (RMC).<sup>h</sup> Paper Yellow Cards are available by writing to either the MHRA or one of the RMCs, and can also be found in copies of the BNF, the Nurse Prescribers' Formulary (NPF), the Monthly Index of Medical Specialties (MIMS) Companion and from the Association of the British Pharmaceutical Industry (ABPI) Compendium of Data Sheets and Summaries of Product Characteristics. Electronic Yellow Cards were introduced in 2002 and can be downloaded from either the MHRA or the RMC websites ([www.yellowcard.gov.uk](http://www.yellowcard.gov.uk)).

<sup>f</sup> The Commission on Human Medicines (CHM) was established on 30 October 2005. It combines the functions of the former Medicines Commission and Committee on Safety of Medicines (CSM). The terms of reference of the CHM include promoting the collection and investigation of information relating to adverse reactions for human medicines to enable advice to be given to health ministers and the Licensing authority on matters relating to human medicines. [www.mhra.gov.uk/home/idcplg?IdcService=SS\\_GET\\_PAGE&nodId=863](http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodId=863)

<sup>g</sup> Thalidomide was first marketed in the UK in 1958, under the trade name Distaval, for the treatment of morning sickness during the early stages of pregnancy. In 1959 the first cases of babies born with congenital malformation of the limbs, known as phocomelia, were reported in Germany. These congenital malformed limbs were also associated with other internal malformations. A causal association with thalidomide was suspected but was strongly refuted by the manufacturer. The number of cases of phocomelia, however, grew rapidly, with an estimated 10,000 cases associated with thalidomide emerging throughout the world, including over 500 cases originating in the UK. Thalidomide was withdrawn from the market in Germany on 27 November 1961 and the UK on 2 December 1961. This was followed by its withdrawal from the majority of countries world-wide over the next nine months. Prior to the thalidomide disaster there was no formal drug regulation system in place to monitor the safety of medicines in the UK. (Report of an Independent Review of Access to the Yellow Card Scheme (2004). TSO, London. [www.mhra.gov.uk/home/groups/comms-ic/documents/websiteresources/con2015008.pdf](http://www.mhra.gov.uk/home/groups/comms-ic/documents/websiteresources/con2015008.pdf))

<sup>h</sup> The Committee on Safety of Medicines Regional Monitoring Centres cover the following regions: Mersey, Wales, Scotland, Northern and Yorkshire and the West Midlands.

The MHRA also receives ADR reports from pharmaceutical companies, which have a statutory obligation to report suspected serious ADRs. If a doctor passes details of an ADR on to the pharmaceutical firm which markets the drug, this information will subsequently be passed on to the MHRA.

### What should be reported via the Yellow Card Scheme?

If it is suspected that a patient has experienced an ADR it should be reported using a Yellow Card. ADRs resulting from prescription medicines, herbal remedies and OTC medications can all be reported. If there is any doubt about whether or not an ADR has occurred and should be reported it is always best practice to submit a report. Causality does not need to have been established.

There are some instances where it is important that all suspected ADRs are reported. These are:

#### Black triangle drugs ▼

When new drugs and vaccines are first marketed they are intensively monitored in order to confirm the risk/benefit profile of the product.<sup>21</sup> Such products are labelled with an inverted black triangle ▼, and healthcare professionals are encouraged to report **all** suspected ADRs which occur as a result of the use of all black triangle drugs regardless of the seriousness of the reaction. Newly marketed drugs will usually be intensively monitored for a minimum of two years. It should be noted, however, that a black triangle is not always removed after this length of time and any medication can be assigned a black triangle if it is considered that it needs to be intensively monitored. For example, black triangle status may be re-assigned to an established product if it is granted a new indication or route of administration, if it is marketed as a new combination with another established active ingredient, or if it is targeted towards a new patient population. If a product is a black triangle drug this will be indicated in the BNF, the NPF, MIMS, and in the ABPI Compendium of Data Sheets and Summaries of Product Characteristics. Advertising material and patient information leaflets (PILs) should also include this information.

A full list of all black triangle products and further information about the black triangle scheme can be found on the MHRA website at [www.mhra.gov.uk](http://www.mhra.gov.uk).

#### Serious reactions

All serious suspected reactions must be reported via the Yellow Card Scheme, regardless of whether a product is a black triangle drug or vaccine. The side effects of an established drug may be well known but if a serious reaction occurs it should **always** be reported so that rare or delayed effects can be identified, more detailed advice can be given on potential side-effects and comprehensive information can be used to compare the relative safety of medicines in the same therapeutic class.

Reactions which are considered serious include those that are:

- fatal
- life-threatening
- disabling or incapacitating
- result in or prolong hospitalisation
- congenital abnormalities
- medically significant.

For example, a review of cases reported via the Yellow Card Scheme, led to the introduction of a statutory, harmonised warning on all aspirin products in October 2003 to highlight the risk of Reye's Syndrome associated with aspirin use in those aged under 16 years.<sup>22</sup> Another example was

the identification of a drug interaction that led to changes in the internationally normalised ratio (INR) values following the concomitant administration of warfarin therapy with cranberry juice.<sup>23,24</sup>

Other examples of serious reactions, given by the MHRA, can be found in appendix C.

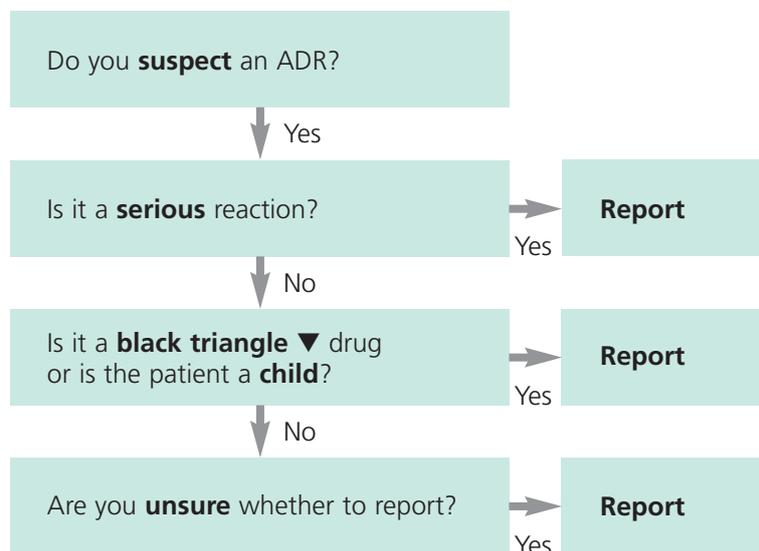
Areas of particular importance to the MHRA for reporting include ADRs in children and the elderly, delayed drug effects, congenital abnormalities and ADRs associated with herbal products.

### ADRs in children

The MHRA asks that all suspected ADRs occurring in children under the age of 18, should be reported regardless of whether the medication is licensed for use in children. Children are often not exposed to medications during clinical trials and many medications are used in children even if they are not licensed for this purpose. This means that monitoring of drug safety is particularly important for this age group.

In 2005 the first BNF for Children (BNFC) was launched which gives 'practical information to help healthcare professionals who prescribe, monitor, supply, and administer medicines for childhood disorders'.<sup>25</sup> This is a vital resource which can improve prescribing to children, and as with the BNF, the BNFC contains useful information that can help with the identification of ADRs. The BNFC clearly indicates whether a medication has a black triangle classification and also contains a few pre-paid paper yellow cards that can be used to report suspected ADRs.

**Diagram 1: Flow diagram to show when an ADR must be reported.**



Source: MHRA, [www.mhra.gov.uk/home/idcplg?IdcService=SS\\_GET\\_PAGE&nodeld=750](http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeld=750) (accessed March 2006)

### **ADRs in the elderly**

Healthcare professionals should be particularly aware that the elderly may be more susceptible to adverse reactions and it is therefore important to monitor drug safety in this age group. Many elderly patients are more likely to be taking multiple medicines and also may metabolise them less effectively or be more sensitive to their effects. A study of hospital admissions published in 2004, showed that the median age of patients admitted with ADRs was 76 years, which was significantly older than those admitted without ADRs (median 66 years).<sup>9</sup> If detected, ADRs in the elderly should be reported according to the protocol outlined above.

### **Delayed drug effects**

Some reactions may become manifest months or years after exposure. Any suspicion of such an association should always be reported to the MHRA. Examples of delayed reactions that might need to be reported include: lipodystrophy resulting from medications prescribed to HIV-infected patients, or any withdrawal reactions caused after a patient has been taking SSRI antidepressants.

### **Pregnancy and congenital abnormalities**

It is vital that all suspected ADRs experienced by women during pregnancy are reported.<sup>26</sup>

In cases where a baby is born with a congenital abnormality or where a pregnancy results in a malformed or aborted foetus and it is suspected that an ADR may be the cause, a Yellow Card should be submitted and this should include information of all medications taken during pregnancy.

### **Herbal medicines**

The popularity of alternative therapies, including herbal medications, is growing. One study in the USA indicated that 10 per cent of adults use herbal medicines.<sup>27</sup> The 'natural' content of herbal therapies means they are often considered to be 'safe' by the public who, along with many professionals, fail to recognise the potential potency of many such products.<sup>3</sup> Patients and healthcare professionals should also be aware that interactions between herbal and other, prescribed or OTC, medications can also cause unexpected reactions. A serious example of this is reduced blood concentrations, which can result from an interaction between the herbal preparation St John's Wort (*hypericum perforatum*) and some commonly prescribed drugs, including warfarin, ciclosporin, oral contraceptives, digoxin, theophylline, and selective serotonin reuptake inhibitors, leading to a loss of drug effect with potentially serious outcomes.<sup>3</sup> The MHRA regulates many herbal medicines but there are still remedies that are available on the market that have not been licensed. It is therefore important that any suspected ADR which occurs from a herbal remedy is reported and that as much information about the ingredients and the source of the remedy are included. In 2002 the CSM advised that the herbal ingredient Kava-kava was associated with rare cases of hepatotoxicity which could be serious in nature.<sup>28</sup> This safety concern led to use of Kava-kava being prohibited in unlicensed remedies.<sup>29</sup>

### **Reclassified medicines**

The number of medications that have been reclassified from prescription only medicines (POMs) to pharmacy (P); and from P to OTC (also known as general sale list (GSL)) has risen in recent years as the government encourages the wider availability of medicines alongside greater patient choice.<sup>3</sup> Before a change in status is granted pharmaceutical companies have to demonstrate levels of safety dependent on specific criteria and provide appropriate prescribing information. Examples of recent POM to P switches include chloramphenicol 0.5 per cent eye drops for the treatment of acute bacterial conjunctivitis and Zocor Heart Pro (simvastatin 10mg) to reduce the risk of a first major coronary event in people who are likely to be at a moderate risk of coronary heart disease (CHD). Clotrimazole for the treatment of *Candidal vulvovaginitis* (thrush) is an example of a P to

GSL switch. With wider availability of these reclassified medicines healthcare professionals, in addition to patients, should pay extra vigilance to their use as rare ADRs or new drug interactions may be identified.

## Patient reporting

Healthcare professionals need to be aware that patients, parents or carers, are now also able to take part in spontaneous reporting of ADRs. This has been introduced in recognition of the fact that the patient is directly affected by an ADR and they may notice features that otherwise go unreported. Patient reporting has not been introduced to replace reports from healthcare professionals but instead should be seen as a mechanism through which the data held by the MHRA can be enriched with patient experiences. Although this scheme is in its early stages, all GP surgeries and community pharmacists should have received information about patient reporting and they are encouraged to make their staff aware that it has been introduced. If a patient experiences an ADR they should also be informed that they may submit a Yellow Card if they wish and information should be available in the surgery or pharmacy about the reporting process.

Patients report suspected ADRs in the same way that healthcare professionals do except that they fill out a different form. Patients can also report suspected ADRs to the Yellow Card hotline, on freephone 0800 1003352. Yellow Card forms are available from GP surgeries, pharmacies and other outlets across the NHS, as well as from the Yellow Card hotline and the MHRA website. The patient reporting section is clearly signposted and includes straightforward information for patients about how and what to report. For further information about medicines that are available in the UK, patients should refer to the website [www.medicines.org.uk](http://www.medicines.org.uk) which lists medicines guides that have been developed as part of the Medicines Information Project. This project aims to encourage patients and the public to make informed choices about their health. It is a collaboration of organisations including the DH, the Royal Pharmaceutical Society, NHS Direct and various voluntary patient organisations.<sup>30</sup>

Despite the introduction of patient reporting, healthcare professionals should continue to report as usual. The benefit of having patient reports is that different information is included or may be presented in a different way and thus a broader picture of the ADR and its impact on the patient can be established. Another advantage of patient reporting is that ADRs resulting from OTC medications, or those that do not result in the patient visiting a doctor might now be reported. It is very important that if a healthcare professional observes an ADR which is serious or which results from a black triangle medication they submit a Yellow Card regardless of whether the patient has also submitted a report.

## How to report an ADR and what happens next

When a Yellow Card is completed by a healthcare professional, information should be included about which drug is suspected to have caused the reaction, the reaction that has occurred, some information about the patient and contact details of the healthcare professional in case further details are required. The patient details which should be included are the sex, age and weight (if known) of the patient. It may be helpful to include the patient's initials and/or a local identification number. The local identification number is any number or code that identifies the patient to the reporter, but not to the MHRA. It should be noted that by supplying these anonymised details a healthcare professional will not breach the confidentiality agreement they have with the patient set out in the Data Protection Act 1998.<sup>31</sup>

Although explicit consent from the patient is not required, it is best practice to inform the patient if a report will be submitted and to keep a copy of the Yellow Card on the patient's notes. Doctors

have an ethical responsibility to ensure that patients are generally aware that ADRs are reported in order to protect the public's health. This could be done, for example, through notices in hospitals and GP surgeries about the Yellow Card Scheme.

Completed Yellow Cards should be submitted either directly to the MHRA or to one of the RMCs, which will then pass the information on to the MHRA. Once a Yellow Card has been received by the MHRA, the person who made the report will be sent an acknowledgement which will quote the unique identification number assigned to the report. Any information which might identify the patient is then removed from the Yellow Card, and the identification number is added. The Yellow Card is then scanned into the MHRA's pharmacovigilance database. MHRA staff also input the anonymised information on to the database in a structured format. The database facilitates the monitoring of ADRs and allows rapid analysis of ADR reports. At any point during this process the reporter may be asked by the MHRA to provide clarification or further information about the ADR. Yellow cards that are received from patients are entered on to the MHRA's medicines safety database and are considered in the context of all other reports received from patients or healthcare professionals for that medicine. Further information for patients about the reporting and follow up processes can be found on the MHRA website.<sup>32</sup>

The pharmacovigilance scientists and physicians at the MHRA use Yellow Card data to detect 'signals' of emerging drug safety problems. They assess the causal relationship between the drugs and reported reactions and identify possible risk factors contributing to the reaction. During this assessment data from other sources may also be referred to, for example:<sup>33</sup>

- case reports in the literature
- pre- and post-marketing clinical trials
- epidemiological studies
- record-linkage databases
- data from other drug regulatory authorities.

When safety hazards are identified, the overall ADR profile for the drug is compared with the 'relevant therapeutic alternatives, and its benefits in terms of efficacy, the therapeutic indication and target patient population(s)'.<sup>33</sup> The CHM (formerly the CSM) and its Pharmacovigilance Expert Advisory Group (PEAG) (formerly the Sub-committee on Pharmacovigilance (SCOP)) advise the MHRA on drug safety so that decisions can be made on whether changes in the use of a medicine are needed. The MHRA also works closely with other European regulatory authorities on pharmacovigilance matters. Regulatory changes may include restrictions in use, reduction in dosage, special warning and precautions. In some instances, where it is considered that the risks of a medicine outweigh the benefits, that medicine may be withdrawn from the market. A study of all the new active substances that were authorised in the UK between 1972 and 1994 showed that 24 out of 583 substances authorised during this period were withdrawn for reasons relating to quality (1), efficacy (1) or safety (22).<sup>34</sup> That corresponds to a withdrawal rate of 3.8 per cent on safety grounds.

## **Communicating information about adverse drug reactions**

An independent review of the Yellow Card Scheme was published in 2004 and made recommendations about ways in which the scheme could be strengthened and how access to Yellow Card data could be improved.<sup>29</sup> As a result of this review it is now possible for healthcare professionals and patients to access complete listings of all of the ADRs that are reported to the MHRA. These data are presented in the form of drug analysis prints (DAP) and include information about what reactions have been reported for each drug. All DAPs and guidance for their interpretation can be accessed via the MHRA website.

For access to more detailed ADR data, systems are being set in place by the MHRA to enable ADR data to be accessed for research and education purposes for the benefit of public health. All requests for ADR data not releasable under Freedom of Information legislation are scientifically reviewed by an independent scientific committee (Independent Scientific Advisory Committee for MHRA Data Research (ISAC) which was established in February 2006) with ethical review provided under the established framework of the Central Office for Research Ethics Committees (COREC) system. For all ADR data requests, consent from a reporter and patient would always be required before access to their data are permitted in line with the provisions of the Data Protection Act, 1998. Further guidance on accessing ADR data for research purposes will be made available on the MHRA website within the first quarter of 2006.

As well as the comprehensive data included in the DAPs, the MHRA communicates with healthcare professionals and patients in a number of ways. Statutory patient information leaflets (PILs) and Summaries of Product Characteristics (SCPs) for healthcare professionals are continually updated with new safety information, while all urgent warnings are communicated in letters sent out to all doctors and pharmacists. The DH also uses the Public Health Link, an electronic cascade system, to disseminate urgent information about ADRs and defective products to healthcare professionals when there is not sufficient time to organise a hard copy mailing.<sup>35</sup> The MHRA and the CHM also produce a regular drug safety bulletin called *Current problems in pharmacovigilance* which is sent to all doctors and pharmacists and is available on the MHRA website. In addition to the freely accessible DAPs, staff at the MHRA provides information on the safety of medicines upon request.

## Reporting other safety problems to the MHRA

It should be noted that the MHRA does not only collect information about adverse reactions to medicines and vaccines. Other safety matters that should be reported to the MHRA include:

### Defective medicines

The MHRA runs the Defective Medicines Report Centre (DMRC) through which complaints and reports of actual and suspected defects in medicines are collected and assessed. Full information about the DMRC and how to submit a report can be found on the MHRA website.

### Adverse incidents involving medical devices

The MHRA receives reports of adverse incidents from both manufacturers and users of medical devices. The Manufacturer Online Reporting Environment (MORE) is an online reporting system for medical device manufacturers and suppliers. The MHRA website can also be used to access online adverse incident reporting forms for medical device users, healthcare professionals, carers, and members of the public. In 2004 8,840 adverse incidents were reported. Recent examples of reported incidents include over-infusion by a syringe pump which could have been potentially life-threatening and a problem with the fixing system for wheelchair backrests which it was found could have caused serious injury. In both instances an investigation found the cause of the fault; consequently a risk alert was issued against use of the pump, and the wheelchair manufacturer made design alterations and upgraded all existing backrests.<sup>36</sup>

### Haemovigilance and the serious adverse blood reactions and events (SABRE) reporting system

Since 2005, the MHRA has been required to collect reports about serious adverse events and serious adverse reactions related to blood and blood components. This is done via a secure online reporting system known as SABRE, to which Blood Establishments and Blood Banks/Hospital Transfusion Teams are able to submit reports. This method of haemovigilance does not replace

local reporting arrangements for non-serious events and Serious Hazards of Transfusion (SHOT) reporting should also continue, although this can be facilitated within the SABRE reporting system. Full guidance and information about SABRE and other UK haemovigilance activities can be found on the MHRA website.

## Structured databases

Drug safety problems are not only assessed through spontaneous reporting but can also be evaluated through the information from large patient databases. Databases which record all events related to the healthcare of a cohort of individual patients or all instances when a particular drug is prescribed are considered to be extremely useful as they represent what happens under normal conditions of clinical practice rather than only recording when a safety problem or adverse reaction occurs.<sup>16</sup> Such databases are important resources for testing hypotheses generated from Yellow Card data.

## General Practice Research Database

A multi-disciplinary team at the MHRA is responsible for the operation of the General Practice Research Database (GPRD). The GPRD is the world's largest database of anonymised longitudinal medical records from primary care.<sup>37</sup> Currently over 300 practices across the UK are registered with the GPRD. The database has three million active patient records and a total of over 35 million patient years of validated data. Participating practices supply the GPRD with a wide range of information covering all aspects of patient care, including use of medications (see box 2). Any GP practice that wants to contribute to the GPRD can apply to do so.

These real-life clinical practice data can be utilised for a range of applications, including clinical trials, drug safety, outcomes research and clinical epidemiology. The large population covered by the GPRD means that it has significant value for pharmacovigilance. The data available include ADRs, co-prescription, co-morbidity, dosage details, off-label prescription, and patient demographics (see appendix D for further details).

### Box 2: Information collected from GPs by the GPRD

- Demographics, including age and sex.
- Medical symptoms, signs and diagnoses, including comments.
- Therapy (medicines, vaccines, devices).
- Treatment outcomes.
- Events leading to withdrawal of a drug or treatment.
- Referrals to hospitals or specialists.
- Laboratory tests, pathology results.
- Lifestyle factors (height, weight, BMI, smoking and alcohol consumption).
- Patient registration, practice and consultation details.

Source: General Practice Research Database, [www.gprd.com](http://www.gprd.com)

There are different levels of access to the GPRD which can be purchased by interested parties under licensing arrangements and a number of services are offered. The GPRD has been used internationally by the pharmaceutical industry, regulators and in academic research. So far, the GPRD has been used to inform over 400 clinical reviews and research papers.

Information about the GPRD, including details of what data are collected and how the database can be accessed, are available on the website, [www.gprd.com](http://www.gprd.com)

## Prescription-event monitoring

The Drug Safety Research Unit (DSRU) in Southampton uses prescription-event monitoring (PEM) to evaluate the safety of newly marketed drugs intended for use primarily in general practice.<sup>38</sup> The DSRU, which is independent of the MHRA and other government offices, uses the hypothesis generating technique of PEM to determine drug safety problems through pharmacoepidemiology.

PEM is an observational cohort technique which collects data on all prescriptions for the first 20,000 to 50,000 patients given a new drug. After a defined period of time, all the doctors who prescribed the new drug are sent a green form on which they are asked to record events reported by the patient subsequent to the prescription. These outcome data then form the basis of the evaluation study. Not all green forms are returned, but the average cohort size is 10,942 for PEM studies. Since the DSRU was established in 1980, PEM studies have been completed for 90 different medications. Whilst those studies that are for regulatory or internal purposes are kept confidential, over 150 scientific publications have so far resulted from the work of the DSRU.<sup>38</sup>

The DSRU website contains information about PEM and also lists the medications that have been monitored to date as well as details of all the work that has been published [www.dsru.org](http://www.dsru.org).

## Other databases

Other databases which are useful for pharmacovigilance and which healthcare professionals should be aware of include:

- **The Tayside Medicines Monitoring Unit (MEMO)** – [www.dundee.ac.uk/memo](http://www.dundee.ac.uk/memo)  
MEMO is a University of Dundee based research collaboration that undertakes research into the safe, effective and cost effective use of medicines and devices as well as helping to improve the understanding of disease, all using anonymised healthcare data.<sup>39</sup> An important feature of MEMO is that it allows record linkage with other datasets, such as those relating to hospital care, which enables a broader understanding of healthcare events or the benefits and risks of particular treatments.
- **The Health Improvement Network (THIN)** – [www.thin-uk.com](http://www.thin-uk.com)  
THIN is a medical research database of anonymised patient records from information entered by general practices in their ViSion systems. Data are supplied to approved researchers for drug safety and epidemiological studies.<sup>40</sup>
- **QResearch** – [www.nottingham.ac.uk/~mczqres](http://www.nottingham.ac.uk/~mczqres)  
The QResearch database is run by Nottingham University. It contains data from 468 general practices throughout the UK with records for 3.3 million current patients and 4 million past patients.<sup>41</sup>

## **Limitations of structured databases**

Despite the strength of the data collected by the GPRD and the DSRU, limitations exist and they are yet to be used to the fullest. The Academy of Medical Sciences has identified areas of research which could benefit significantly from greater use of these existing databases including maternal drug exposure on pregnancy outcome, neonatal and early childhood health, and the use of medicines in children.<sup>16</sup>

Both GPRD and PEM only collect information from general practice and thus there are significant gaps in collection of data from secondary care, where more complex medications tend to be used and where the potential for serious ADRs to occur is therefore greater. A lack of financial incentive results in at least 30% of GPs choosing not to return the green cards used in PEM which creates the potential for bias in the data. The Academy of Medical Science notes that the effects of this bias are unknown.<sup>16</sup>

The high price of using the GPRD is likely to be prohibitive to some research groups. Access to these data ranges from between £7,000 and £60,000 for datasets to cover a single research question to between £27,500 and £300,000 per year for varying degrees of online access.<sup>42</sup> It is worth noting, however, that the Medical Research Council (MRC) has now acquired access to the GPRD for the benefit of the UK research community.<sup>43</sup> The MRC hopes to encourage high quality research in public health and primary care by providing an opportunity for UK-based researchers to access to the GPRD datasets. Information about the MRC, the conditions of their GPRD license and the eligibility requirements for researchers wishing to access the GPRD in this way, can be found on the MRC website at [www.mrc.ac.uk](http://www.mrc.ac.uk).

# The UK and international pharmacovigilance

## The European Medicines Agency and EudraVigilance

The European Medicines Agency (EMA) was set up in 1995 to ensure the safe and effective use of Centrally Authorised Medicines, that is, those medicines which are authorised throughout the European Union. EudraVigilance, a data processing network and management system is one method used by the EMA to coordinate monitoring of these medicines.<sup>44</sup> It was launched in December 2001 to facilitate the collection of information about ADRs. Requirements are set out in Council Regulation (EEC) 2309/93 and Commission Directive 2000/38/EC. The MHRA, as the UK's Competent Authority, must send details of all serious UK ADR reports it receives from any health professional or pharmaceutical company to the EudraVigilance database within 15 days of receiving the report.<sup>29</sup> Reports are also received from the pharmaceutical industry. The mechanisms for electronic reporting are still being developed and there are yet questions to be resolved regarding access to the database and ensuring patient confidentiality. Currently the European Commission, EMA and EU Competent Authorities have full access to the EudraVigilance database and pharmaceutical companies have limited access. Individual doctors, pharmacists and patients do not have access, although this may change as the system is developed.

For further information about EudraVigilance see its website at <http://eudravigilance.emea.eu.int>

## World Health Organisation (WHO) Programme for International Drug Monitoring

The World Health Organisation (WHO) Programme for International Drug Monitoring is operated by the Uppsala Monitoring Centre, in Sweden. The programme allows collaboration in monitoring drug safety between participating countries.<sup>45</sup> The monitoring centre was established in 1968, and consists of a network of National Centres for pharmacovigilance. Box 3 below summarises the functions of the WHO monitoring programme. At present there are 79 member countries in the programme, and a further 18 associate members. The designated National Centre in each member country submits individual case reports of suspected ADRs to be stored in a common database. The MHRA is the UK's designated National Centre. The WHO database currently holds around 3.4 million ADR case records and thus can be a rich data source for pharmacovigilance. Access to these data is, however, limited primarily to National Centres.

Further information about the WHO programme can be found on its website at [www.who-umc.org](http://www.who-umc.org).

### Box 3: Functions of the WHO Programme for International Drug Monitoring

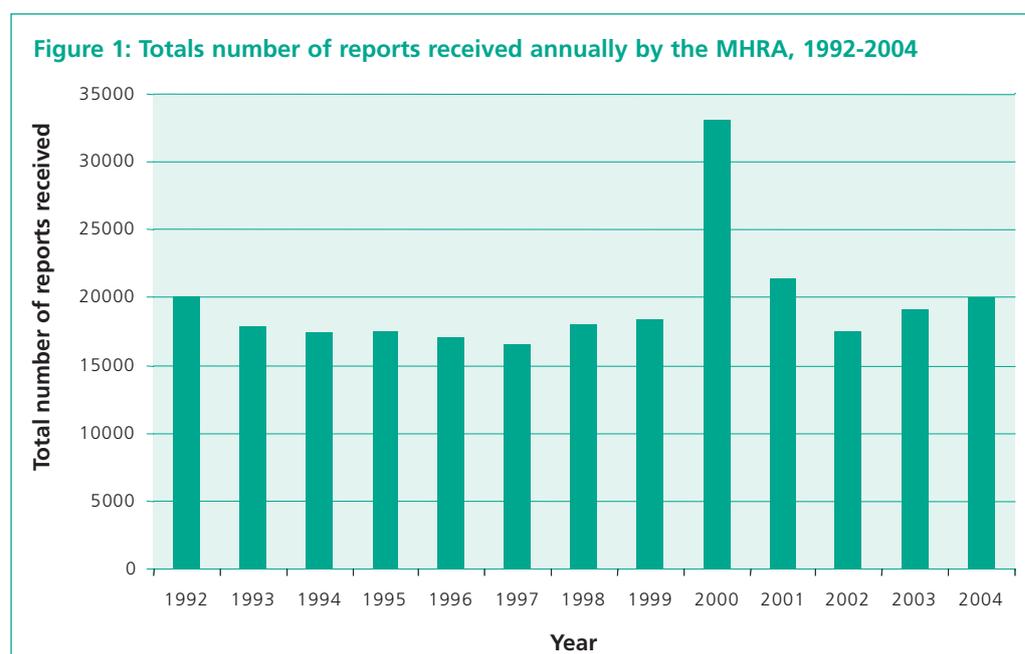
- Identification and analysis of new adverse reaction signals from the case report information submitted to the National Centres, and from them to the WHO database.
- Provision of the WHO database as a reference source for signal strengthening and ad hoc investigations.
- Information exchange between WHO and National Centres.
- Publication of WHO Pharmaceuticals Newsletter and Uppsala Reports.
- Provision of training and consultancy support to National Centres and countries establishing pharmacovigilance systems.
- Computer software for case report management designed to suit the needs of National Centres (Vigibase Online).

Source: WHO Programme for International Drug Monitoring, [www.who-umc.org](http://www.who-umc.org)

## Why is the rate of spontaneous reporting so low?

The main strength of the Yellow Card spontaneous reporting scheme is that it enables continual monitoring of the use of a product throughout its life span and by all patients.<sup>46</sup> Despite the fact that the scheme is well-established and Yellow Cards have become more widely accessible in recent years, ADRs are greatly under-reported and the number of reports received annually by the MHRA has remained fairly consistent at around 20,000 since the mid-1980s (see figure 1 for number of reports from 1992-2004). The exception to this was in 2000, when a significant increase in the number of reports was associated with a mass meningitis C vaccination campaign for all children under 18 years of age.<sup>29</sup> Compared to other countries the number of spontaneous reports submitted in the UK is relatively high and reporting rates in relation to prescription volumes are also among the best in Europe.<sup>2</sup> It is estimated, however, that only 10 per cent of serious reactions and between 2 and 4 per cent of non-serious reactions are reported.<sup>2</sup> Such a high level of under-reporting will necessarily lead to bias in the data collected via the Yellow Card Scheme.

PEM data, collected by the DSRU, raise the question about whether healthcare professionals are fully aware of the need to monitor black triangle drugs more closely and to report all ADRs caused by them. One PEM analysis of 15 newly marketed drugs, showed that while ADRs were five times more likely to be reported if the reaction was serious rather than non-serious, only 9 per cent of the ADRs found by PEM had been reported to the Committee on Safety of Medicines (CSM), indicating significant under-reporting via the Yellow Card Scheme.<sup>47</sup>



Source: Data supplied by the MHRA.

A 1976 discussion by Dr Bill Inman, who pioneered the Yellow Card Scheme, highlighted 'Seven deadly sins'<sup>1</sup> that might cause the low reporting rate of ADRs among healthcare professionals.<sup>48</sup> As the scheme has become better established and accessible most of the problems identified by Inman have been overcome. One more recent survey of UK healthcare professionals showed that the only 'sin' still affecting reporting of ADRs was 'lethargy'.<sup>49</sup> Doctors and other healthcare professionals have many demands on their time and it is appreciated that they are required to carry out many tasks during the working day and thus finding the time to complete Yellow Cards may be difficult. It is important, however, that healthcare professionals recognise the importance of spontaneous reporting of suspected ADRs and the vital contribution that this can make to pharmacovigilance and maximising drug safety. In order, therefore, to enhance patient care it is crucial that healthcare professionals make every effort to submit a Yellow Card in accordance with the relevant guidelines whenever appropriate. As well as time pressures, the above survey identified both a lack of available Yellow Card forms and a belief that ADRs should only be reported if causality was certain as other reasons for the low reporting rate.

While the introduction of electronic Yellow Cards should have improved access to the scheme, other studies have also highlighted a disinclination among healthcare professionals to report an ADR if they are uncertain of the link between the reaction and a medication.<sup>50,51,52</sup> The beliefs that serious adverse reactions will be identified in clinical trials<sup>51</sup> and that there is no need to report a well known reaction<sup>16,52</sup> are also noted in the literature. Box 4 shows the reasons given in an attitudinal survey of Dutch physicians for not reporting ADRs. Anecdotal evidence also points to a fear by professionals that reporting a suspected ADR via the Yellow Card Scheme may result in them being legally liable for any consequences of the reaction.<sup>11</sup> This fear may, for example be particularly pertinent when medicines that are unlicensed for use by children have been prescribed to a patient under the age of 18. Healthcare professionals should be reassured that the MHRA would never allow Yellow Card data to be used for legal or disciplinary purposes.

#### Box 4: Results of an attitudinal survey of Dutch physicians regarding voluntary reporting of ADRs

- Only 26% knew which ADRs to report.
- 93% thought the reaction was too well known.
- 75% thought the reaction was trivial.
- 72% were uncertain whether the reaction was caused by a drug.
- 38% did not have enough time.
- 36% thought that reporting was too bureaucratic.
- 22% did not know how to report.
- 18% were not aware of the need to report ADRs.

Source: Elland I, Belton, K & van Grootheest A et al (1999) Attitudinal survey of voluntary reporting of adverse drug reactions, *British Journal of Clinical Pharmacology* **48**: 623-7.

<sup>1</sup> The 'Seven deadly sins' as described by Dr Inman are summarised by Belton K, Lewis S & Payne S et al (1995) as: ignorance ('I am unsure how to report'), diffidence ('I may appear foolish about reporting a suspected ADR'), fear ('I may expose myself to legal liability by reporting an ADR'), lethargy ('I am too busy to report ADRs'), guilt ('I am reluctant to admit I may have caused harm'), ambition ('I would rather collect cases and publish them') and complacency ('only safe drugs are marketed').

Although it is true that many adverse reactions may be well documented, it is important that all serious suspected ADRs and those occurring with black triangle products are always reported so that the benefit/harm profile of a medication can be kept up to date and so that comprehensive advice about prescribing and drug safety can be communicated to all healthcare professionals. Healthcare professionals should be reminded that if they are in any doubt as to the causality of a reaction or whether or not they should submit a Yellow Card, then it is best practice that they should submit a report.

Improving reporting rates of ADRs is primarily about improving awareness of the need to report and the mechanisms used to submit a Yellow Card. In areas that are served by an RMC, which engages in work with the local reporting population and in awareness raising activities, reporting rates are higher than in areas where there is no regional centre.<sup>29</sup> Doctors and other healthcare professionals have a duty to keep their knowledge and skills up to date, which can be done by participating in continuing professional development (CPD). As pharmacovigilance is an area where awareness and participation levels can be poor, there could be an expansion of CPD activities which explore the importance of reporting ADRs. One controlled study (2005) looked at the impact of a distance-learning package in pharmacovigilance which was linked to educational credits on the rate and quality of reporting.<sup>53</sup> The results showed that, at least in the short term, Yellow Card reports from those that passed the course assessment increased in number and improved in quality compared to those who had not taken the course. This indicates that CPD could have a crucial role to play in improving the collection of Yellow Card data.

Improved and more consistent undergraduate teaching of the need to report ADRs, as well as the wider importance of pharmacovigilance, are identified in one study as being crucial if a reporting culture within the medical profession is to develop.<sup>54</sup> This research also advocates a more involved role for the MHRA in promoting the Yellow Card Scheme to undergraduate medical, pharmacy and nursing students. In 2003 a paper which discussed the teaching of safe and effective prescribing in UK medical schools highlighted the importance of incorporating clinical pharmacology into the core curriculum.<sup>55</sup> It states that the core knowledge and understanding of medical students should include the following about ADRs:

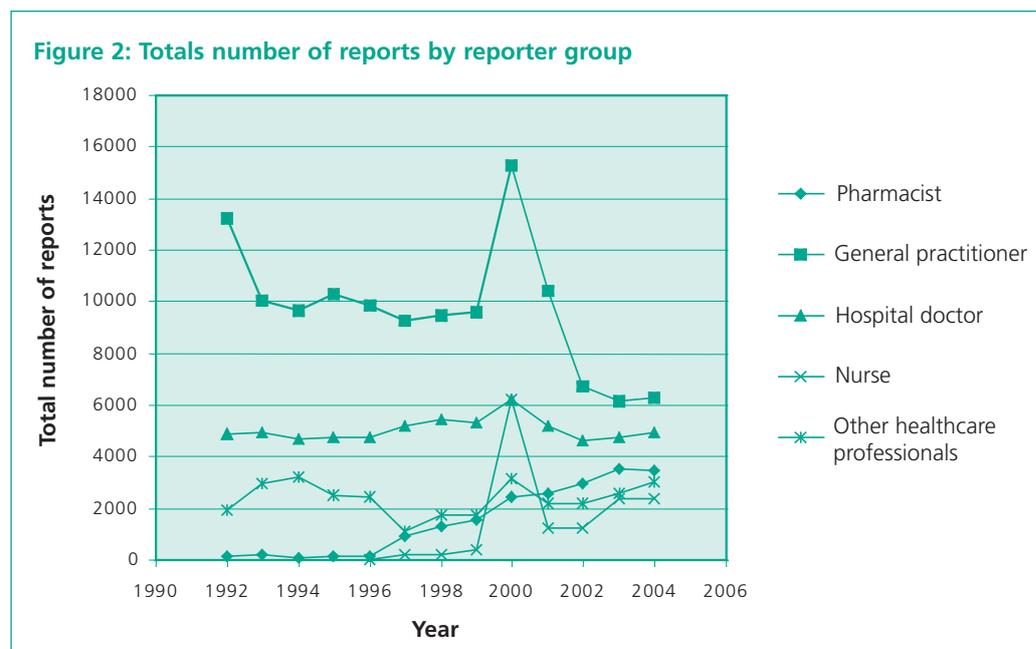
- types and mechanisms of ADRs
- the frequency of ADRs in primary and secondary care
- recognition of the predisposing factors and how risks can be minimised
- the importance of reporting ADRs and the role of the Yellow Card scheme.

As well as a lack of awareness, a breakdown in communication can also result in ADRs either not being identified and/or not being reported. Patients can be prescribed medications in many different healthcare settings across primary and secondary care, including GP surgeries, NHS walk-in centres, hospitals or treatment centres, as well as private medical settings. Poor communication between healthcare professionals, for example between hospitals and general practice, can result in it being difficult for drug therapies to be monitored effectively.<sup>56</sup> It is vital that patient records and correspondence are both accurate and thorough so that all healthcare professionals are well informed and there is consistency in the care that is provided.

Communication between doctors and patients is also critical in identifying suspected ADRs and can help prevent some ADRs occurring.<sup>12</sup> Research published in 2004 showed that health professionals rarely record the use of complementary and alternative medicines in a patient's history.<sup>57</sup> It is crucial that patients are asked what medications they are taking, and that particular reference is made to OTC medications and all other non-prescribed therapies, such as herbal remedies or those purchased over the internet. Further, when presented with unexpected or unexplained symptoms consideration should be given to the fact that the patient may have

experienced an adverse reaction to one or more medications that they have been taking. When prescribing or administering medications it is vital that the prescriber gives clear instructions about taking the medication, requests that the patient reads the patient information leaflet which includes information about side effects that they may experience, and also finds out whether the patient is taking any other medication that may interact with the proposed treatment. Effective communication is needed so that the healthcare professional has as much information as possible and that the patient is fully informed about their medications and any possible side effects. Healthcare professionals may find the British Heart Foundation's factfile on *Communicating Risk to Patients*, a useful resource.<sup>58</sup> It can be downloaded from its website, [www.bhf.org.uk](http://www.bhf.org.uk).

General practitioners (GPs) have traditionally submitted the highest proportion (around 60 per cent) of Yellow Cards (see Figure 2), and it is often accepted that GPs may be best placed to report ADRs. It can be seen from the graph, however, that in recent years the proportion of reports being submitted by nurses and pharmacists has been increasing (also see appendix E). This increased participation by other healthcare professionals is valued by the regulatory authorities and analysis of reports made by nurses and pharmacists has shown that their involvement can be very useful.<sup>19,20</sup> The contribution that nurses can make to the Yellow Card scheme was particularly evident during the meningitis C vaccination campaign in 2000. It should be noted, however, that given the high incidence of ADRs in hospitalised patients, hospital doctors could make a greater contribution to ADR reporting. Doctors should be reminded that the introduction of nurse and pharmacist reporting was meant to supplement the reports made by doctors and not be a substitute for them. Figure 2 shows that the number of reports received from GPs in the last few years has been significantly lower than in previous years. There has not yet been any research into why this has occurred although speculation might pin point increased workload and administration or a presumption that others are reporting as possible reasons for this decline.



Source: Data supplied by the MHRA

While it is not considered that making reporting of ADRs mandatory would combat under-reporting,<sup>50</sup> the development of the national NHS IT system NPfIT represents an opportunity for information on ADRs to be systematically collected through centrally held patient records.<sup>16</sup> The technology office of NHS Connecting for Health has been in discussions with the MHRA about ways in which electronic Yellow Cards can be incorporated into the new system and about the interaction between the GPRD and the Secondary Uses Service (SUS) of NPfIT.<sup>59</sup> In relation to the GPRD a broader discussion about the capture of primary care data is anticipated, while prescription data should be brought into the SUS when the electronic transmission of prescriptions is rolled out, starting in early 2007. Such developments could prove significant for the future effectiveness of pharmacovigilance, particularly in secondary care where monitoring at present is underdeveloped. While this could transform ADR reporting in England, it is equally important that similar mechanisms for capturing such information are developed in the other devolved nations.

# Conclusion

Given the limitations of clinical trials in identifying rare and delayed ADRs, and the need for comprehensive drug safety profiles, the importance of reporting ADRs cannot be overemphasised. The pharmacovigilance systems in place in the UK are well established and present excellent opportunities for generating signals about potential drug hazards. These systems can only be successful, however, if they are utilised effectively and if awareness of their importance is continually highlighted. Under-reporting of ADRs via the Yellow Card Scheme is one area where significant improvements are needed in pharmacovigilance. The following recommendations are suggested ways in which healthcare professionals can build on the good work that is already being done.

# Recommendations

- It is the professional duty of all healthcare professionals to report all suspected ADRs associated with black triangle products and all serious ADRs associated with established products using the Yellow Card Scheme. If there is any uncertainty about whether a report should be submitted it is best practice to report the ADR. The experts assessing the report can then decide if further investigation is needed.
- All reports should be as comprehensive as possible, as quality data are essential in order to inform drug safety analysis. To improve the quality of online reports, an applicable pre-populated template should appear when either a healthcare professional or a patient fills out an electronic Yellow Card.
- All healthcare professionals should be vigilant to the status of medicines, particularly those labelled as black triangle medications which are under intensive monitoring, and changes to the classification of such medications such as pharmacy availability of former prescription only medicines.
- Healthcare professionals should not be deterred from reporting by the recently introduced provision for patients to report suspected ADRs via the Yellow Card Scheme. It should be noted that the database used by the MHRA can identify and deal with any duplicate reports.
- When prescribing medication, doctors should inform patients that should they suffer any reaction to a medication, they should inform the prescribing doctor and/or complete a patient Yellow Card which is available on the MHRA website.
- Patient information (leaflets etc) should be widely available in clinics in primary and secondary care explaining how patients can report ADRs.
- It is important that prescribers routinely ask patients about OTC medicines or herbal remedies they are using. This is particularly important in avoiding interactions which are a significant cause of ADRs.
- Effective communication between healthcare professionals is essential, as are comprehensive medical notes, in order that doctors in different care settings have access to all the relevant information about a patient's medical history.
- NPfIT represents a significant opportunity to systematically gather information on ADRs and improve pharmacovigilance. Collection of ADR data should form part of the SUS of the IT systems being developed for the NHS. Similar mechanisms for capturing such data should be developed in the devolved nations.
- The methods and importance of pharmacovigilance should be covered more comprehensively and systematically in the undergraduate medical curricula. CPD courses relating to pharmacovigilance should be offered to healthcare professionals. Patient experiences, as captured by the MHRA database of patient reports, could be used to inform this training.
- Given the intensive monitoring of black triangle medications, it is vital that the importance of reporting ADRs is reinforced within all CPD courses relating to new drug developments.
- The MHRA should commission research to improve the understanding of the barriers to reporting ADRs and how they may be overcome. Specifically, research should be carried out to understand why Yellow Card reporting by GPs has fallen over the last 10 years.

# Sources of further information

*This listing of organisations is intended as a guide for those wishing to know more about reporting ADRs. The BMA is not responsible for the content of external websites, nor does it endorse or otherwise guarantee the veracity of statements made in non-BMA publications.*

## Spontaneous reporting of ADRs

### Medicines and Healthcare products Regulatory Agency (MHRA)

Market Towers  
1 Nine Elms Lane  
London  
SW8 5NQ  
Email: [info@mhra.gsi.gov.uk](mailto:info@mhra.gsi.gov.uk)  
[www.mhra.gov.uk](http://www.mhra.gov.uk)

Address to request or submit a Yellow Card:  
MHRA  
CSM Freepost  
London  
SW8 5BR

Patient Yellow Card hotline: 0808 1003352

### CSM Mersey

Freepost  
Liverpool  
L3 3AB  
[www.liv.ac.uk/~druginfo/csm/](http://www.liv.ac.uk/~druginfo/csm/)

### CSM Wales

Freepost  
Cardiff  
CF4 1ZZ  
<http://medweb.cf.ac.uk/csm/>

### CSM Scotland

51 Little France Crescent  
Old Dalkeith Road  
Edinburgh  
EH16 4SA  
[www.show.scot.nhs.uk/CSMScotland/](http://www.show.scot.nhs.uk/CSMScotland/)

### CSM Northern and Yorkshire

Freepost  
Newcastle-upon-Tyne  
NE1 1BR  
[www.nyrdtc.nhs.uk/](http://www.nyrdtc.nhs.uk/)

### CSM West Midlands

Freepost  
Birmingham  
B18 7BR  
[www.csmwm.org](http://www.csmwm.org)

## Structured databases

### General Practice Research Database (GPRD)

General Practice Research Database Division  
Medicines and Healthcare products  
Regulatory Agency  
15th Floor, Market Towers  
1 Nine Elms Lane  
London  
SW8 5NQ  
Email: [admin@gprd.com](mailto:admin@gprd.com)  
[www.gprd.com/home](http://www.gprd.com/home)

### Drug Safety Research Unit (DSRU)

Drug Safety Research Unit  
Bursledon Hall  
Blundell Lane  
Southampton  
SO31 1AA  
Email: [georgina.spragg@dsru.org](mailto:georgina.spragg@dsru.org)  
[www.dsru.org](http://www.dsru.org)

### Tayside Medicines Monitoring Unit (MEMO)

Ninewells Hospital and Medical School  
Dundee  
Scotland  
[www.dundee.ac.uk/memo](http://www.dundee.ac.uk/memo)

### The Health Improvement Network (THIN)

The Bread Factory  
1A Broughton Street  
London  
SW8 3QJ  
[www.thin-uk.com](http://www.thin-uk.com)

### **Q Research**

The Division of Primary Care  
13th Floor  
Tower Building  
University of Nottingham  
NG7 2RD  
[www.nottingham.ac.uk/~mczqres](http://www.nottingham.ac.uk/~mczqres)

## **International ADR reporting**

### **EudraVigilance**

Email: [eudravigilance@emea.eu.int](mailto:eudravigilance@emea.eu.int)  
[www.eudravigilance.org](http://www.eudravigilance.org)

### **WHO Programme for International Drug Monitoring**

Uppsala Monitoring Centre  
Stora Torget 3  
S-753 20  
Uppsala  
Sweden  
[www.who-umc.org](http://www.who-umc.org)

## **Patient and other information**

### **Medicines.org.uk**

[www.medicines.org.uk](http://www.medicines.org.uk)  
Email: [info@medicines.org.uk](mailto:info@medicines.org.uk)

### **NHS Direct**

0845 4647  
[www.nhsdirect.nhs.uk](http://www.nhsdirect.nhs.uk)

### **Medical Research Council**

20 Park Crescent  
London  
W1B 1AL  
[www.mrc.ac.uk](http://www.mrc.ac.uk)

# Appendix A

## Clinical trials process for drugs

Clinical trials for pharmaceutical products are carried out in four phases, only moving from one phase to the next if the previous phase has shown promising results. The four 'ideal' phases are as follows:

- Phase I – the drug is tested on a small number of healthy volunteers to test how it is metabolised, whether it is safe for humans and to find the best way of administering the treatment.
- Phase II – a small number of patients are given the drug to test for side effects, activity and optimum dose, and to start comparing it to the current treatment or a placebo.
- Phase III – the drug is given to a larger group of patients for continued testing of safety and efficacy and to compare it with the current treatment or a placebo. These trials are nearly always randomised.
- Phase IV – this phase occurs once the drug has been licensed and checks for possible long-term side effects of the drug. It is also known as post-marketing surveillance.

The extract above is taken from the BMA clinical trials internet resource which can be found at [www.bma.org.uk/ap.nsf/Content/Hubclinicaltrials](http://www.bma.org.uk/ap.nsf/Content/Hubclinicaltrials)

## Appendix B

Some major safety issues identified through the Yellow Card Scheme

Year	Medicine	Adverse reaction	Resulting action
1995	Tramadol (Zydol ▼*)	Psychiatric reactions	Warnings
1995	Cyproterone acetate (Cyprostat, Androcur)	Dose-related hepatotoxicity	Restricted indications, requirement for monitoring of liver function
1995	Quinolone antibiotics	Tendinitis, tendon rupture	Improved warnings
1995	Tacrolimus (Prograf ▼*)	Hypertrophic cardiomyopathy	Warnings, dose reduction and monitoring requirements
1996	Alendronate (Fosamax ▼*)	Severe oesophageal reactions	Warnings and revised dosing instructions
1997	Clozapine (Clozaril)	GI obstruction	Improved warnings
1997	HIV protease inhibitors	Hyperlipidaemia and fat redistribution	Improved warnings and monitoring recommendations
1998	Isotretinoin (Roaccutane)	Psychiatric reactions	Improved warnings
1998	Sertindole (Serdolect ▼*)	Sudden cardiac death	Drug withdrawn**
1999	Human clottable protein concentrate (Quixil ▼*)	Fatal neurotoxic reactions following unlicensed use in neurosurgery	Improved warnings
1999	Aristolochia in Chinese herbal remedies	Renal failure	Aristolochia banned
2000	Cisapride (Prepulsid, Alimix)	Serious cardiovascular reactions	Use of Cisapride suspended in the UK***
2001	Bupropion (Zyban ▼*)	Seizures	Improved warnings and revised dosing instructions
2003	Kava-kava	Hepatotoxicity	Supply of Kava-kava prohibited in the UK

\* Black Triangle (▼) drug at the time the major safety issue was identified

\*\* Sertindole was reinstated in 2002 with increased warnings

\*\*\* Cisapride licences have been cancelled

Source: MHRA (2004) Report of an Independent Review of Access to the Yellow Card Scheme.

# Appendix C

## Examples of serious ADRs

### Blood

Bone marrow dyscrasias  
Coagulopathies  
Haemolytic anaemias

### Cardiovascular

Arrhythmias  
Cardiac arrest  
Cardiac failure  
Cardiomyopathy  
Circulatory failure  
Hypertension  
Hypotension  
Myocardial  
Ischaemia/infarction  
Sudden death

### Central nervous system

Anorexia nervosa  
Catatonia  
Cerebrovascular accident  
Coma  
Confusional state  
Dependence  
Depression  
Epilepsy (inc exacerbations)  
Extrapyramidal reactions  
Hallucinations  
Hyperpyrexia  
Intracranial pressure  
Myasthenia  
Neuroleptic malignant

### Gastrointestinal

Colitis  
Haemorrhage  
Hepatic cirrhosis  
Hepatic dysfunction  
Hepatic fibrosis  
Ileus  
Pancreatitis  
Perforation  
Peritonitis (inc fibrosing)  
Pseudo-obstruction

### Immunological

Anaphylaxis  
Arteritis  
Drug fever  
Lupus syndrome  
Graft rejection  
Polyarteritis nodosa  
Vasculitis

### Malignancy

Any

### Metabolic

Acidosis  
Adrenal dysfunction  
Diabetes  
Hypercalcaemia  
Hyperkalaemia  
Hyponatraemia  
Hypokalaemia

### Musculoskeletal

Arthropathy  
Aseptic bone necrosis  
Osteomalacia  
Pathological fracture

### Renal

Renal dysfunction  
Urinary retention

### Reproduction

Spontaneous abortion  
Antepartum haemorrhage  
Congenital abnormalities  
Eclampsia, pre-eclampsia  
Infertility  
Uterine haemorrhage,  
perforation

### Respiratory

Alveolitis (allergic, fibrosing)  
Bronchospasm (inc  
exacerbation)  
Pneumonitis  
Respiratory failure  
Thromboembolism

### Skin

Angioedema  
Bullous eruptions  
Epidermal necrolysis  
Exfoliation (generalised)

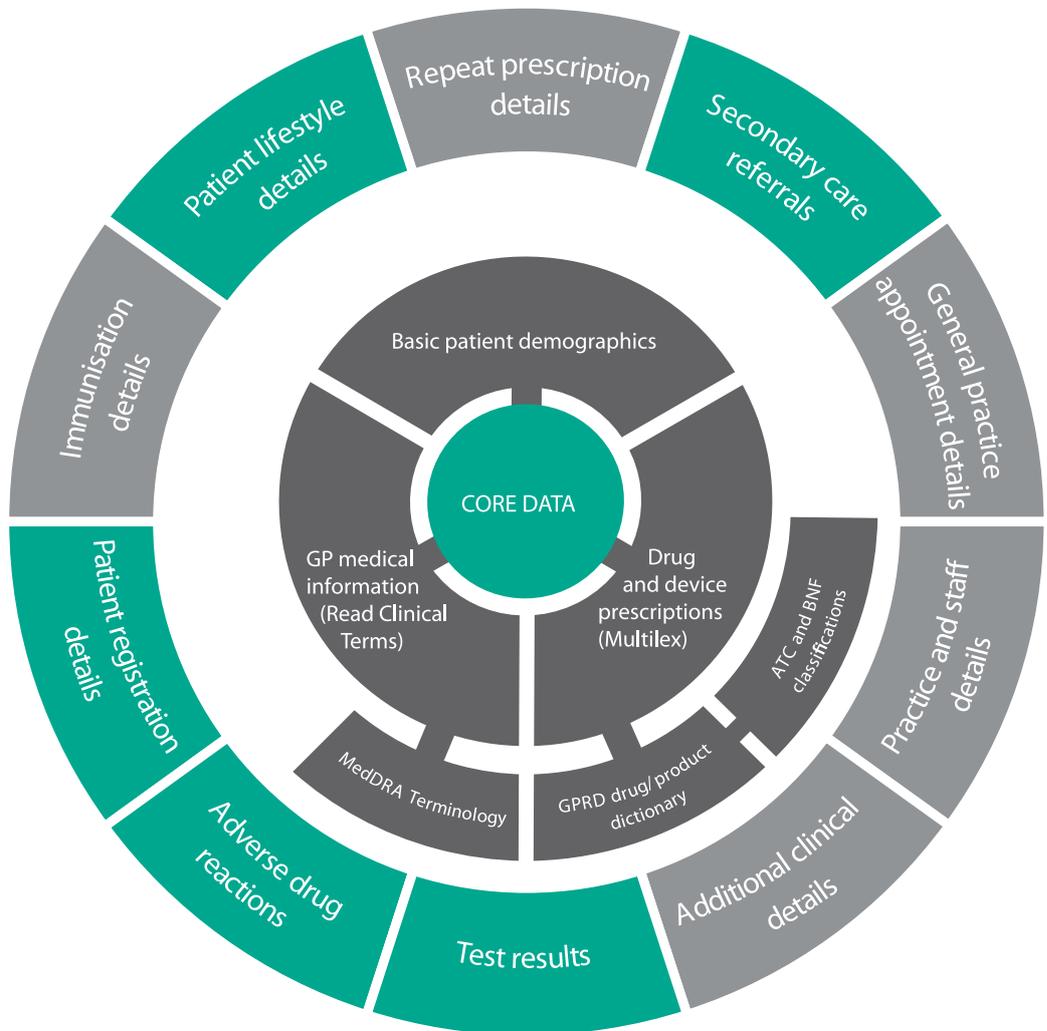
### Special senses

Cataract

Source: MHRA website at [www.mhra.gov.uk/home/idcplg?IdcService=SS\\_GET\\_PAGE&nodId=752](http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodId=752)

## Appendix D

Information held by the General Practice Research Database which can be used for pharmacovigilance.



Source: GPRD, Pharmacovigilance information sheet. [www.gprd.com](http://www.gprd.com)

# Appendix E

## Yellow Card data

### Number of suspected adverse drugs reactions reports on the ADROIT database received from 01.07.1991 – 31.07.2005

Received year	Reports with serious adverse reactions	Reports associated with black triangle drugs	Reports associated with herbal products	Reports where patient age is specified as 65 and over (elderly)	Reports where patient age is specified as less than 18 years	Total number of reports
1991*	5,076	41	20	2,680	713	10,351
1992	9,865	158	43	4,630	1,772	20,136
1993	9,156	240	31	3,834	2,447	18,035
1994	9,256	123	25	3,801	2,522	17,522
1995	9,830	210	28	3,909	1,818	17,640
1996	9,530	359	36	3,914	1,583	17,107
1997	9,659	418	46	4,204	1,436	16,627
1998	10,463	512	41	4,657	1,470	18,053
1999	10,574	803	66	4,541	2,675	18,483
2000	15,112	4,082	143	5,528	12,332	33,152
2001	12,693	5,433	80	5,082	1,712	21,461
2002	11,549	2,535	72	4,828	1,634	17,619
2003	12,742	3,965	77	5,233	2,500	19,246
2004	13,665	5,214	92	5,419	2,198	20,021
2005*	8,758	4,150	54	3,206	1,571	12,924

### Source of reports – who reported

Received Year	Reports from pharmacists	Reports from general practitioners	Reports from hospital doctors	Reports from nurses	Reports from other healthcare professionals	Reports from patients	Total number of reports
1991*	23	6,526	2,678		1,124		10,351
1992	149	13,205	4,846		1,936		20,136
1993	179	9,992	4,944		2,920		18,035
1994	68	9,614	4,632		3,208		17,522
1995	100	10,304	4,755		2,481		17,640
1996	101	9,831	4,743	21	2,411		17,107
1997	901	9,254	5,195	193	1,084		16,627
1998	1,285	9,465	5,412	195	1,696		18,053
1999	1,513	9,604	5,270	388	1,708		18,483
2000	2,431	15,254	6,179	6,171	3,117		33,152
2001	2,534	10,378	5,144	1,227	2,178		21,461
2002	2,907	6,687	4,596	1,232	2,197		17,619
2003	3,515	6,142	4,700	2,365	2,524		19,246
2004	3,421	6,265	4,941	2,388	3,006		20,021
2005*	2,021	3,238	3,173	1,742	2,319	431	12,924

Source: Data supplied by MHRA

\*Note: data provided for 1991 and 2005 are not for the complete years.

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