

# Report of an Independent Review of Access to the Yellow Card Scheme

April 2004

London: TSO



Published by TSO (The Stationery Office) and available from:

**Online**

[www.tso.co.uk/bookshop](http://www.tso.co.uk/bookshop)

Mail, Telephone, Fax & E-mail

TSO

PO Box 29, Norwich, NR3 1GN

Telephone orders/General enquiries: 0870 600 5522

Fax orders: 0870 600 5533

E-mail: [book.orders@tso.co.uk](mailto:book.orders@tso.co.uk)

Textphone 0870 240 3701

**TSO Shops**

123 Kingsway, London, WC2B 6PQ

020 7242 6393 Fax 020 7242 6394

68-69 Bull Street, Birmingham B4 6AD

0121 236 9696 Fax 0121 236 9699

9-21 Princess Street, Manchester M60 8AS

0161 834 7201 Fax 0161 833 0634

16 Arthur Street, Belfast BT1 4GD

028 9023 8451 Fax 028 9023 5401

18-19 High Street, Cardiff CF10 1PT

029 2039 5548 Fax 029 2038 4347

71 Lothian Road, Edinburgh EH3 9AZ

0870 606 5566 Fax 0870 606 5588

**TSO Accredited Agents**

(see Yellow Pages)

*and through good booksellers*

© Crown Copyright 2004

All rights reserved.

Applications for reproduction should be made in writing to the Copyright Unit, Her Majesty's Stationery Office, St Clements House, 2-16 Colegate, Norwich NR3 1BQ.

First published 2004

ISBN 0 11 703409 6

Printed in the United Kingdom for The Stationery Office

# CONTENTS

<b>Foreword</b>	<b>v</b>
<b>Summary</b>	<b>1</b>
<b>1 Introduction and history of the Yellow Card Scheme</b>	<b>15</b>
1.1 Background to the Review	15
1.2 Principles of the Yellow Card Scheme	16
1.3 History of the Yellow Card Scheme	19
1.4 Extensions to the Yellow Card Scheme	20
1.5 EudraVigilance	31
<b>2 Methodology</b>	<b>33</b>
2.1 Steering Committee for the Review	33
2.2 Consultation exercise	34
2.3 The report	35
<b>3 Consultation issues</b>	<b>39</b>
3.1 Public health	39
3.2 Scientific research	41
3.3 Genetic research	43
3.4 Conditions and levels of access to Yellow Card data	45
3.5 Scientific appraisal	48
3.6 Ethics	49
3.7 Controls on research use of Yellow Card data	51
3.8 Consent	55
3.9 Audit	59
3.10 The independent scientific committee; membership functions, responsibilities and conditions for research access	62
3.11 Legal and operational issues	65
3.12 Patient reporting	70
3.13 Strengthening of the Yellow Card Scheme	73
3.14 Implementation of changes	80
3.15 Other issues	80

<b>4</b>	<b>Recommendations</b>	<b>83</b>
	<b>Bibliography and references</b>	<b>93</b>
	<b>Glossary of terms and acronyms</b>	<b>97</b>
	<b>Annexes</b>	<b>107</b>
	<b>Annexes within the Report</b>	<b>107</b>
	Annex A: Yellow Card	109
	Annex B: Steering Committee membership	111
	Annex C: Sir Derrick Dunlop letter of 1964 to all UK doctors	113
	Annex D: Press release – announcement by Lord Warner	115
	Annex E: Consultation letter (minus annexes)	117
	Annex F: List of key stakeholder meetings	121
	Annex G: ADR reports received by year via the Yellow Card Scheme since 1964	123
	<b>Annexes on the MHRA website</b>	
	<a href="http://medicines.mhra.gov.uk/ourwork/monitorsafequalmed/yellowcard/accessreviewreport.htm">http://medicines.mhra.gov.uk/ourwork/monitorsafequalmed/yellowcard/ accessreviewreport.htm</a>	
	Annex H: Annexes of Consultation letter	
	Annex I: Consultation responses	
	Annex J: Report of the Working Party on Adverse Reactions. June 1983	
	Annex K: Report of the Working Party on Adverse Reactions. July 1985	
	Annex L: Minutes of meetings of the Steering Committee	

# FOREWORD

## Introduction

The Review was instigated to respond to the increasing number of requests from individuals and organisations outside the Medicines and Healthcare products Regulatory Agency (MHRA) for access to the Yellow Card database.

Since 1964, when the Yellow Card Scheme began, the analysis of the information contained in the Yellow Cards (Annex A) has been undertaken almost entirely in house by the MHRA staff, and its predecessor organisations.

While the primary purpose of the Review is to identify the conditions under which data from individual Yellow Cards might be released by the MHRA, this objective could not be realised without at the same time considering how the Yellow Card Scheme could be improved and strengthened for the future benefit of patients and public health. In this context, the responses received during the Review have been unanimous in emphasising the importance and value of the Scheme.

## The continuing importance of the Yellow Card Scheme

The need for a system to identify unexpected adverse effects of new therapeutic drugs and medicines has been illustrated many times. Chloroform, as the first anaesthetic, was superseded because of the risk of sudden death, when ether and other safer anaesthetics were developed. Streptomycin was hailed as the first drug for tuberculosis until the side effect of permanent deafness was identified. Some of the early polio vaccines actually transmitted the disease they were intended to prevent.

The Yellow Card Scheme was prompted by the thalidomide disaster and in the forty years of the Scheme, other unexpected effects have been identified from drugs that had been carefully tested and evaluated before being licensed for general use. There can be no guarantees that unexpected effects, some serious others less so, will not follow the licensing of a new drug. Indeed, some rare effects may only be identified from prolonged monitoring. For newly licensed drugs in particular, but also for older products, **vigilance is essential by all involved** if side effects are to be identified.

When an unexpected effect is identified, the Yellow Card Scheme is there to provide a straightforward route for MHRA to be alerted.

### **Terms of Reference**

The Terms of Reference of the Review are set out on page 15. The issues involved are complex and, for their proper resolution, a multidisciplinary approach is essential. For this reason a Steering Committee was convened and the membership is set out in Annex B.

### **Access to Yellow Card data**

The main outcome of the Review is the recommendation that, subject to compliance with the conditions which are described in the report, the MHRA should provide independent researchers with access to the Yellow Card database.

### **Patient reporting**

Although patient reporting is not mentioned in the Terms of Reference, the patient is the person most directly affected by an unexpected effect of a medicine. Patients may notice features that otherwise go unreported. In some circumstances the patient's experience has been crucial. This is why a recommendation of the Review is that patient reporting should be introduced and the methods for this should be investigated.

### **Structure of the report and procedures**

The Report is in four chapters, with a summary, glossary and seven annexes within the report and another five annexes available on the MHRA website <http://medicines.mhra.gov.uk/ourwork/monitorsafequalmed/yellowcard/accessreviewreport.htm>

The Summary includes the main conclusions and recommendations. These should not be read in isolation but in the context of the relevant narrative sections of the report in Chapter 3.

Chapter 1 provides the introduction to the Review and sets out the history of the Yellow Card Scheme.

Chapter 2 describes the methodology of the Review.

Chapter 3 discusses the issues about which stakeholders were consulted, and the conclusions and recommendations of the Steering Committee.

Chapter 4 lists all the recommendations from Chapter 3 including those which, for brevity, were not included in the Summary. However, all deserve attention in their own right.

**The Steering Committee believes their recommendations, which reflect the views of the wide range of stakeholders, provide a set of scientifically and ethically robust procedures through which the MHRA can provide independent researchers with access to a uniquely valuable dataset.**

### **Acknowledgements**


As Chairman of the Steering Committee, I am indebted to all members of the Committee. This report would not have been possible without their specialist knowledge and experience. Our discussions were always constructive.

Before the Committee could develop any responses to the Terms of Reference, it was necessary to identify the key problems which the MHRA wished the Review to address. In this task the Steering Committee welcomed the help of Dr June Raine, Director of the Post Licensing Division of the Agency. Having identified the Agency's issues for the Review it was essential to discover the views of the wide range of stakeholders about these issues and other aspects of the Yellow Card system that stakeholders wished to draw to our attention.

On behalf of the Steering Committee, I wish to thank the many health professionals, professional bodies, patients' organisations, academic researchers, the pharmaceutical industry, and members of the media whose contributions have helped us with our challenging task.

The Steering Committee was fortunate in the secretariat the MHRA provided for our work. Our secretaries Mr Jeremy Mean, Dr Bridget Jennings and Miss Amanda Lawrence were all indispensable and Dr Jennings earned our sincere gratitude for collating our multidimensional discussions and preparing this Report. The Committee would like to thank Mrs Judith Peachey for editing the Report to meet a very tight publication schedule.

Dr Jeremy Metters CB

A handwritten signature in black ink, appearing to read 'J Metters', with a stylized flourish at the end.

19th April 2004

# SUMMARY

## INTRODUCTION

The Yellow Card Scheme was introduced in 1964 to **provide a straightforward route for a doctor or dentist to report a suspicion that a medicine could have harmed a patient**. Sir Derrick Dunlop, Chairman of the Committee on Safety of Drugs (CSD), emphasised that the Scheme's purpose was to gather reports of suspected adverse drug reactions (ADRs)<sup>1</sup>, Annex B. Proof of a causal link is not required. Sir Derrick set out the basic principles which have stood the test of time, see Table 1.

**Table 1 Fundamental principles of the Yellow Card Scheme**

- A voluntary scheme based on the good will of reporters
- The collation of reports of ADRs without a causal link needing to be established
- Reporters are encouraged to report without delay
- All reports are held in complete confidence by the MHRA and CSM
- The data are never to be used for disciplinary purposes or for enquiries about prescribing costs

The CSD was the forerunner of the Committee on Safety of Medicines (CSM). The Scheme is now run by the MHRA on behalf of the CSM, and is designed to detect signals that indicate that the safety of a product requires further investigation. This structure imposes limitations upon the uses to which data from it can be put for research (section 3.2.1).

Over 40 years, nearly 500,000 reports have been received. From these reports some serious ADRs that required urgent regulatory action, and other less serious ADRs, have been identified.

Initially, reports were requested only from doctors and dentists but the Scheme is now open to reports from coroners, pharmacists and, more recently, nurses (section 1.4.5). An important current issue is whether patients should be allowed to submit reports (section 1.4.5 (iv)).

Chapter 1 describes the history and operation of the Scheme.

---

<sup>1</sup> Throughout the Report suspected adverse drug reactions (ADRs) will be referred to as ADRs



## **THE REVIEW: ITS TERMS OF REFERENCE AND SCOPE**

### **Requests for access to Yellow Card data**

The Review was initiated 'by an increase in requests from outside the MHRA for access to Yellow Card data which raise major issues in relation to public health'. Lord Warner announced the Terms of Reference in a Parliamentary statement on 21 July 2003, Annex D. The primary purpose is to consider the circumstances and conditions in which the MHRA should release data from the Scheme for independent research and public health purposes.

### **Other issues considered during the Review**

The opening of the Scheme to reports from patients (section 3.12).

What can be done to improve the quality and frequency of ADR reporting rates (section 3.13).

What will be the consequences of MHRA's commitment to contribute UK data to the new EU pharmacovigilance system (EudraVigilance) (section 3.11.4).

What are the implications of the Freedom of Information (FOI) Act for MHRA in 2005 (section 3.11.3).

### **Matters excluded from the scope of the Review**

The Review did not address the MHRA's internal processing of Yellow Cards as this is the subject of an internal review.

## **THE REVIEW'S PROCEDURES AND METHODS**

### **The Steering Committee**

A multidisciplinary Steering Committee was convened to advise and direct the Review, Annex B. Members of the Committee were invited to serve in a personal capacity (Chapter 2).

### **Consultation with stakeholders**

A consultation letter, Annex E with H, was sent to a very wide range of stakeholders on 6 October 2003. The written consultation ended on 9 January 2004 and 55 responses were received, Annex I. Twenty-four meetings were held with representatives of the stakeholders, Annex F. All stakeholders' proposals have been discussed by the Committee.

The procedures of the Review are described in Chapter 2.

## **THE RELEASE OF YELLOW CARD DATA BY MHRA**

Requests for Yellow Card data take many different forms and their acceptability depends on the type of data requested. Since 2000, to comply with the Data Protection Act 1998<sup>2</sup>, reporters have been told not to include the patient's name, date of birth or other identifying personal details on Yellow Cards. Instead, reporters now enter a unique identifier, patient initials and age. The release of anonymous aggregated data presents few problems whereas the release of information from individual Yellow Cards must be considered in the context of its proposed use.

### **Categories of Yellow Card data**

To facilitate discussion the Steering Committee considered the benefits, risks and implications of releasing data at three levels of detail:

- I Aggregated anonymous data collated from individual Yellow Cards;
- II Data that include details from individual Yellow Cards, but without any information that identifies a reporter or patient or provides any opportunity for the recipient to contact a reporter;
- III Data initially similar to Category II but where the intention is to conduct research that would involve contact with the reporter and/or the patient. If approved, requests in Category III would enable the researcher to ask to be put in contact with the reporter. (For reasons set out in section 3.8, the MHRA must make the initial contact to find out if the reporter is prepared to be contacted.)

### **Freedom of Information Act and the release of data in Category I**

The Freedom of Information Act will, in 2005, require MHRA to release on request aggregated anonymous data in Category I, section 3.4.1.

### **Stakeholder concerns about the release of data in Categories II and III**

Stakeholders insist that, whatever the intended purpose, requests for data in these categories must be rigorously evaluated. Recipients of these data must understand the important limitations on their interpretation and use.

Yellow Cards report suspected but unproven ADRs. Some reported ADRs will prove to be mistaken. The number of genuine ADRs that go unreported is unknown. The exact number of patients who receive the same medicine, the denominator, is unknown. Therefore, in the absence of reliable numerators and denominators, rates of ADRs cannot be derived from Yellow Card data.

---

<sup>2</sup> <http://www.hmsso.gov.uk/acts/acts1998/19980029.htm>

Stakeholders pointed to the danger that false conclusions could be reached about the safety of a medicine if these constraints were not recognised. Such erroneous conclusions would harm the Yellow Card Scheme and have adverse effects on public health.

### **Scientific and ethical review**

Most stakeholders agree that their concerns would be satisfied if the essential safeguards of review by independent scientific and ethics committees are applied to requests for data in Categories II and III.

Reasons for scientific appraisal and ethical review are described in sections 3.5 and 3.6 respectively.

## **THE STEERING COMMITTEE'S CONCLUSIONS**

**There was considerable agreement between stakeholders and the Steering Committee on many issues.** This simplified the Committee's task in preparing the Conclusions and Recommendations that follow.

### **I THE VALUE, IMPORTANCE AND COVERAGE OF THE SCHEME**

The Scheme remains essential for monitoring the safety of medicines in the UK. Any changes made must not harm the Scheme or reduce reporting rates. The Scheme should continue as the single UK-wide route for reporting ADRs to MHRA and CSM. It has unanimous support from stakeholders as an invaluable system for identifying signals of previously unsuspected ADRs.

#### **The basic principles of the Scheme**

The original principles, as set out in Sir Derrick Dunlop's 1964 letters to doctors and dentists (Table 1), should continue unchanged. There is no support from stakeholders for any change to these principles.

Anonymity and confidentiality remain essential unless and until the reporter and the patient have given their consent to disclosure.

#### **Submission of Yellow Cards**

The voluntary principle of the Scheme should remain unchanged (experience of legal compulsion in other countries has not proved successful in raising ADR reporting rates). No fee should be paid to the reporter for submission of Yellow Cards, see also Recommendations 15–17 below.

### **Patient consent**

The patient's consent is not necessary prior to submission of a Yellow Card by a health professional. Cards are anonymous and the event reported is one of 'suspicion', not proof. Nevertheless, it would be good practice for reporters to inform a patient when a Yellow Card is submitted unless this is not practical or not considered to be in the patient's best interests.

## **II RELEASE OF DATA**

To maximise the public health benefit, data from the Scheme should be released to organisations and individuals outside MHRA for research and public health purposes, but controls must be in place. On this central issue, there was almost complete unanimity among stakeholders.

### **Management of data release**

The Steering Committee believes that the following procedures will facilitate the release of data and avoid misuse and erroneous conclusions being drawn because the constraints of the data are not understood. The procedures are designed to:

- (i) give confidence to reporters that the information they provide in Yellow Cards will be used responsibly;
- (ii) maintain patient anonymity and confidentiality;
- (iii) encourage an increase in ADR reporting;
- (iv) maximise the data that can be made available;
- (v) apply fairly and equitably to all applicants who request Yellow Card data;
- (vi) be transparent.

These procedures are shown diagrammatically in the flow chart at Figure 1, page 13.

### **Aggregated anonymised data sets**

The MHRA should take the initiative and proactively publish data covered by FOI on a regular basis, see Recommendation 3 and section 3.4.1.

### **Scientific review of requests for data from individual Yellow Cards**

The release of data that includes information about unnamed individual patients may present data protection and/or ethical issues. All requests for data that fall outside the criteria for routine disclosure under FOI should be considered by scientific and ethics committees independent of MHRA, see Recommendations 4–9 and section 3.4.1.

It would be disproportionate to oblige the scientific committee to consider every application. Some straightforward requests for access in Category II could be authorised without recourse to scientific and ethical review if they fulfilled a predetermined set of published criteria, see Recommendations 6 and 7.

### **Ethics review**

The well established ethical principles for research involving patients must apply. A properly constituted ethics committee must consider all requests for data access that might involve contact between a researcher and the reporter, to obtain further information about the patient, or to make contact with the patient, for example to obtain a blood sample.

The ethics of research in the NHS are subject to approval by Main Research Ethics Committees (Main RECs). In view of the national coverage of the Yellow Card Scheme, the Main RECs are best placed to consider the ethics of Yellow Card research, Recommendation 9, section 3.6.

### **Genetic research**

Genetic research using Yellow Card data will require ethical approval. The principles for genetic research, that have been set out by the Human Genetics Commission, must be applied, Recommendations 10, 11 and section 3.3.

### **Access to the whole database and on-line access**

Any requests for access to the whole database and/or for on-line access should be considered by the scientific committee and Main REC on their scientific merits and ethical acceptability.

Real-time on-line access to any part of the database should not be approved for two reasons. A time interval is essential for MHRA to take any necessary regulatory action and, for Data Protection purposes, to remove personal information that may have been included by mistake.

### **Contact with the reporter**

When the scientific committee and Main REC have authorised proposals that involve the researcher contacting the reporter, this contact must be made by MHRA. The researcher should on no account be given the name of the reporter until the MHRA has established that (s)he is willing to assist with the proposed research. 'Cold calling' by researchers to reporters is not acceptable.

**Patients' consent for research**

The well established rules for patients to participate in research must apply. The reporter is best placed to explain the research to a patient. The reporter must be free to decide whether a patient should be approached. If a patient declines, that decision must have no bearing on the patient's future care.

**Publication of research findings**

Before publication<sup>3</sup> of any Yellow Card research, researchers who have been given individual Yellow Card data must be required contractually to inform the MHRA, scientific committee and Main REC of their plans for publication or dissemination of their findings into the public domain, and provide a draft of their proposed publication.

This delay is essential so that the MHRA can consider any necessary regulatory or public health implications and, when appropriate, inform the relevant Marketing Authorisation Holders (MAHs).

**Reimbursement of reporters' expenses and fees**

Health professionals have a duty to report ADRs that they observe in their patients. The present position that no fee is paid to reporters for submission of Yellow Cards should be maintained.

Reimbursement commensurate to the work involved should be provided by the research sponsor to reporters for their time and effort, Recommendations 15–17, section 3.11.5.

**III IMPROVING THE SCHEME'S ABILITY TO IDENTIFY NEW SIGNALS****Improving reporting rates**

There are no easy solutions. Since the start of the Scheme there has been recurring criticism of the low proportion of ADRs that are reported. The voluntary nature of the Scheme is cited as a reason for this. Experience in other countries with mandatory ADR reporting has shown that legal and other forms of compulsion are not effective in improving reporting rates. A mandatory Scheme is not recommended by the Steering Committee, section 3.15.2.

**Clarification of which ADRs should be reported**

There may be uncertainty among reporters about which ADRs should be reported. The CSM and MHRA should reinforce and clarify their advice on the types of ADR that health

---

<sup>3</sup> Publication includes all forms of media (documents, television scripts, via the Internet etc.)

professionals should report. The emphasis should be on serious ADRs and previously unrecognised ADRs. There will be little added value from increasing the number of reports of well recognised less serious ADRs. Recommendations 18, 20, section 3.13.3.

### **Better professional education and information**

A comprehensive education and information strategy is needed to draw attention to the importance of the Scheme, Recommendation 20, and section 3.13.2.

The Scheme is rarely or inadequately covered in undergraduate and postgraduate education of doctors or other health professionals, section 3.13.1.

### **Feedback from the Scheme to reporters**

The Regional Monitoring Centres have demonstrated that better feedback to reporters has been effective in raising the profile of the Scheme and in increasing reporting rates, Recommendations 20, 22 and section 3.13.5.

### **Electronic reporting**

Electronic transmission of data in other fields is now normal procedure. While ADRs can be reported on-line to MHRA, this route deserves more publicity. Its potential to facilitate reporting should be maximised, section 3.13.2.

### **Opening the Scheme to all health professions**

With the widening of prescribing to other health professions, through independent and supplementary prescribing and via patient group directions (PGDs) (section 1.4.5 (i)), it is essential that every health professional is aware of the Scheme. It will become increasingly important for all health professionals to report ADRs.

### **Patient reporting**

The Scheme has not provided a way for patients to report experiences that they attribute to ADRs. A pilot study of indirect patient reporting through NHS Direct has been in progress since April 2003, but with disappointing results. Organisations representing patients' interests want patients to be able to report their experiences direct to MHRA, and almost all stakeholders agree.

The Steering Committee is convinced that a system should be set up for patients to report directly to MHRA, Recommendation 23, section 3.12. Initially, there should be a parallel system to collate reports from health professionals and patients separately until pilot studies have identified the best method for collecting patient reports.

## **Regional Monitoring Centres (RMCs)**

Regional Monitoring Centres (RMCs) provide an educational and information function that improves local reporting rates (section 3.13.5). There is evidence that where RMCs are active, reporting rates are higher due to this function and the fact that they offer feedback to reporters. Their educational potential could be further exploited to increase understanding of the Scheme to doctors and other health professionals.

To avoid confusion, all Yellow Cards should in future be submitted direct to MHRA and not via RMCs, as now happens in some places. MHRA should send RMCs all Yellow Cards received from their individual geographical areas.

Within the single UK Yellow Card Scheme, the RMCs in Edinburgh and Cardiff have, respectively, an important responsibility to provide information relevant to the devolved health responsibilities of the Scottish Parliament and Welsh Assembly.

## **Implementation of changes and pilot studies**

Prior to implementation, the MHRA should discuss the changes recommended in this report, and the reasons for them, with health professionals and with patient organisations. Some recommendations can be developed through pilot studies, Recommendation 24.

## **MAIN RECOMMENDATIONS**

### **Basic principles**

- 1 The basic principles of the Scheme, as set out in Sir Derrick Dunlop's letters in 1964, should not be changed. Any new uses of Yellow Card data should strengthen the Scheme but must not put its future at risk.

### **Access to data**

#### **Release of data**

- 2 The MHRA should open access to the Yellow Card database and should maximise the release of data from the Scheme for independent research, subject to appropriate safeguards.

#### **Freedom of information; aggregated anonymised data sets**

- 3 Wherever possible, anonymised aggregated data should be regularly published on the MHRA website accompanied by guidance on interpretation. Other data sets that are not regularly published should be available on request, under FOI.



### **Scientific review of requests for data from individual Yellow Cards**

- 4 Requests for data not subject to FOI and for data from individual Yellow Cards should be assessed by an independent scientific committee set up by the Licensing Authority for this purpose.
- 5 The committee should consider all proposals under the same set of rules, irrespective of their origin.
- 6 The committee should establish a set of criteria for the release of data by MHRA to straightforward applications that satisfy the criteria. These criteria must not permit the release of reporter or patient identifiers.
- 7 The scientific committee should publish the criteria and its other rules of procedure, and prepare an annual report for the Licensing Authority.
- 8 An appeal mechanism should be available to applicants who believe their proposals have been refused without good reason.

### **Ethics Review**

- 9 A Main REC must be consulted about any proposed research that may involve access to a patient or procedures that require consent, including personal information about the patient known to the reporter, or other procedures that under normal conditions require ethical approval.

### **Genetic and specialised research**

- 10 When the scientific committee receives a research proposal that includes genetic or other specialised research, the committee must ensure that it has amongst its membership sufficient experience and/or expertise to assess a research proposal involving any aspects of genetics, or co-opt a person with appropriate experience. The same principle applies to other specialised research.
- 11 The ethical principles established by the Human Genetics Commission must apply to all forms of genetic research.

### **Access to the entire database and on-line access.**

- 12 Requests for access to the entire database for research on 'signal detection', and/or for on-line access to the database, should be considered by the scientific committee and the Main REC. While such requests may be infrequently authorised by these committees, access must be delayed until the MHRA has had time to consider any regulatory and/or data protection issues.

### Contact with the reporter for the patient's consent for research

- 13 When the scientific committee and the Main REC authorise proposed research that requires contact between the researcher and the reporter, the MHRA must make the initial contact with the reporter.

### Publication of research findings

- 14 All researchers should be contractually required to notify MHRA, the scientific committee and the Main REC of their plans to publish or disseminate research findings based on Yellow Card data, and provide copies of any proposed publications or other forms of presentation. MHRA should inform the relevant Market Authorisation Holders (MAHs). Notification and pre-publication copies of reports should be provided 28 days in advance.

### Reimbursement of reporters' expenses and fees

- 15 Reimbursement of expenses should be made to reporters who assist in research based on Yellow Cards.
- 16 There should be a scale of charges for researchers accessing Yellow Card data that is not subject to FOI. This should be published on the MHRA website. The level of charges should relate to the volume of work involved.
- 17 The MHRA should set up an administrative system to manage the research procedures and the reimbursement of expenses. This system should be cost neutral to the Agency.

## STRENGTHENING THE SCHEME

- 18 It is essential for the Scheme to maintain its focus upon serious ADRs and black triangle (▼) products, but greater clarity is required about the meaning of 'serious' and which other categories of ADRs should be reported.

To improve the Scheme's capacity to identify ADRs, MHRA should consider what emphasis should in future be given on receiving Yellow Card reports on:

- off label use of licensed products;
- products whose legal status has changed;
- ADRs that are not mentioned in SPCs and PILs.

- 19 More publicity should be given to electronic reporting of ADRs. Reporters should be encouraged to use this method.

- 20 The MHRA should develop a communication strategy to improve professional and public education and provision of information about the Yellow Card Scheme. This must clarify:
- the types of ADRs that should always be reported;
  - the role of Regional Monitoring Centres;
  - local feedback to reporters where there is no RMC;
  - how all those with an interest in emerging ADRs can obtain up-to-date information.
- 21 Information and professional education about the Scheme should be addressed to health professionals involved in independent and supplementary prescribing.

### **Regional Monitoring Centres**

- 22 RMCs should be more closely integrated in the Scheme. The type of feedback provided by RMCs should be tried in other places to raise reporting rates. Reporters in areas covered by the RMCs should be made aware of their functions and that information from Yellow Cards within each RMC's geographical area will be shared between the MHRA and the RMC in order to increase local reporting rates.

### **PATIENT REPORTING**

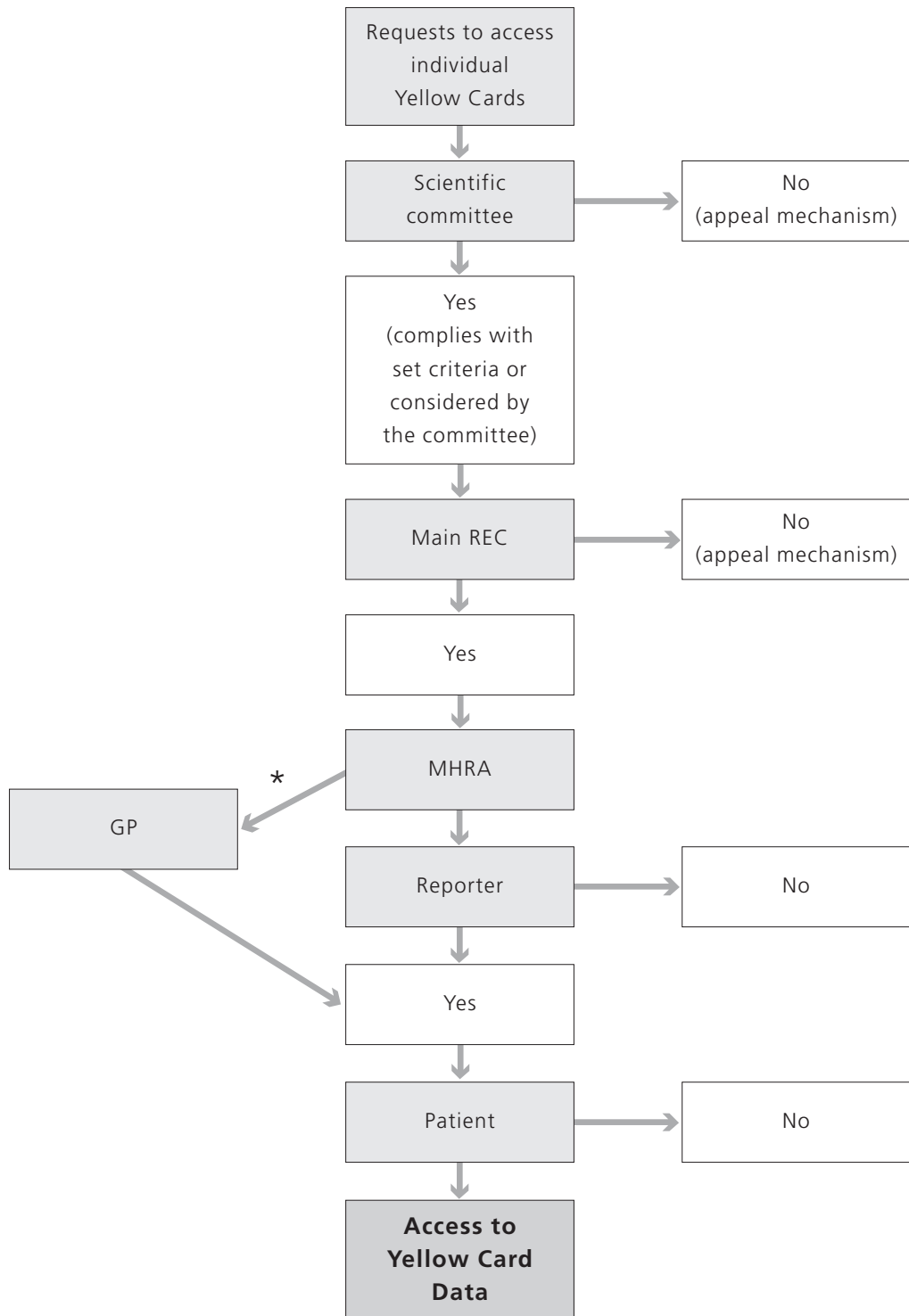
- 23 A system should be set up for patients to report ADRs directly to the MHRA. Different approaches to patient reporting should be tried but, initially, patient reports should be kept separate from those of health professionals through a parallel system until experience indicates the best method of linking patient and Yellow Card reports to the same ADR.

### **IMPLEMENTATION OF CHANGES**

- 24 Pilot studies should be undertaken to identify the best ways of raising ADR reporting rates and to inform and educate health professionals and patients about the Scheme. Direct patient reporting systems, as proposed by stakeholders, can also be tested through local pilot studies.

*A full list of recommendations is provided at Chapter 4.*

**Figure 1 Review process for requests for Yellow Card data involving the reporter and/or patient consent**



\* The normal pattern would be for the MHRA to contact the reporter to ask whether they consent for their details to be passed to the researcher. If the reporter agrees, the researcher can then contact the patient through the reporter for consent for further information and/or investigation. When the reporter is not the prescriber or when it is appropriate for the GP to be informed, the MHRA should contact the GP with the request for patient consent for access to the data (section 3.8.2). This will be either using the contact details on the Yellow Card or through the original reporter.

# 1 INTRODUCTION AND HISTORY OF THE YELLOW CARD SCHEME

## 1.1 BACKGROUND TO THE REVIEW

On 21 July 2003, the Parliamentary Under Secretary of State for Health (Lords), Lord Warner, announced an independent Review of the 'Yellow Card Scheme'. The Yellow Card Scheme, which was initiated 40 years ago and operated by the Medicines and Healthcare products Regulatory Agency (MHRA) and Committee on Safety of Medicines (CSM), collates reports of suspected adverse drug reactions (ADRs)<sup>4</sup> from health care professionals and acts as an early warning system for the MHRA and CSM of possible drug safety hazards.

The Department of Health press release announcing the Review is attached at Annex D and includes the terms of reference of the Review:

- To identify and describe the range of issues which should be considered when considering access to data generated by the Yellow Card Scheme including
  - ethical
  - operational
  - financial and
  - statutory (including open Government/Freedom of Information (FOI)).
- To identify relevant stakeholders to the scheme and to define how such interests arise.
- To consider in what circumstances access to the data generated by the scheme could be said to be in the public interest and the extent to which this falls within existing legal provisions.
- To make proposals for guiding principles and a mechanism for handling such requests.
- To make recommendations for action.
- The Review should report to the Chairman of the MHRA by the end of 2003.

The MHRA and its predecessors have traditionally released anonymised aggregated Yellow Card data upon request. However, in recent times, established approaches to use of the Yellow Card database have been tested, with requests being received for use of the database for research and audit purposes.

---

<sup>4</sup> Throughout the Report suspected adverse drug reactions (ADRs) will be referred to as ADRs

Some of these requests were above and beyond the established policy on access, primarily for research purposes, but also included the wider interests of the Department of Health and the National Health Service (NHS). These ranged from reports on classes of medicines to copies of the whole database for genetics research, the creation of a DNA databank and for the development of methodologies for identifying potential drug safety signals. The MHRA also received requests for access to, and analysis of, the Yellow Card data electronically from remote sites, use of the data for European research funding applications and originator location details of Yellow Cards for the purposes of audit.

Use of the Yellow Card data to minimise the current burden of ADRs and unlock the potential of so called 'designer medicines' was raised following the Government's Genetics White Paper. These changing demands on the Yellow Card Scheme raised important ethical, operational and financial issues in relation to public health. Ministers agreed that the time had come for a review of access to Yellow Card data to consider whether, and under what conditions and for what purposes, the data should be made more widely available. This should coincide with the fortieth anniversary of the Scheme.

## **1.2 PRINCIPLES OF THE YELLOW CARD SCHEME**

The UK Licensing Authority responsible for medicines for human use is a body of Ministers consisting of the Ministers of Health and Agriculture, including the Secretary of State for Health. The MHRA is an Executive Agency of the Department of Health, which acts on behalf of the Licensing Authority.

The MHRA is responsible for protecting and promoting public health and patient safety by ensuring that medicines, healthcare products and medical equipment meet appropriate standards of safety, quality, performance and effectiveness, and are used safely<sup>5</sup>. The MHRA was formed from a merger of the Medicines Control Agency (MCA) and the Medical Devices Agency (MDA) on 1 April 2003. Throughout this text the MHRA is used to refer to the Agency and its predecessors.

In order to obtain a marketing authorisation (MA) or to license a new medicine, signs of quality, safety and efficacy have to be demonstrated. Initially, knowledge of the safety profile of the new medicine will be limited to the more common adverse drug reactions (ADRs) as the medicine will have been tested in a relatively small number of patients in clinical trials, which may be as few as 1,500 patients for a new chemical entity. Once the medicine is licensed and used in normal clinical practice, greater numbers of patients are exposed in a less controlled environment where unexpected, rarer and sometimes serious side effects may be observed for the first time.

---

<sup>5</sup> <http://www.mhra.gov.uk>

As all effective medicines have the potential to cause side effects, it is vital that the safety of all medicines is monitored in routine clinical practice throughout their marketed life. One way to do this is to collect reports of ADRs via a spontaneous reporting scheme.

In the UK, the MHRA collates data on ADRs via the Yellow Card Scheme from doctors, dentists, coroners, pharmacists and nurses working in the NHS and for private health providers. Reports are received directly from them and via pharmaceutical companies. The Scheme is voluntary for health professionals but pharmaceutical companies have legal obligations to report ADRs to the MHRA (Waller *et al*, 1996).

The Yellow Card Scheme is only one of several data sources used to monitor licensed medicines in the UK but it plays a pivotal role in monitoring the safety of medicines and has contributed to making the UK one of the leading drug regulators in the world. Since its launch in 1964 (section 1.3.1), around 500,000 reports have been received by the MHRA and the CSM, its independent scientific advisory body.

**Table 2 Some major safety issues identified through the Yellow Card Scheme**

<b>Year</b>	<b>Medicine</b>	<b>Adverse reaction</b>	<b>Resulting action</b>
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 United Kingdom***
2001	Bupropion (Zyban▼)	Seizures	Improved warnings and revised dosing instructions
2003	Kava-kava	Hepatotoxicity	Supply of Kava-kava prohibited in the United Kingdom

\* 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

The Yellow Card Scheme assists in alerting the MHRA and CSM to new signals (or potential safety concerns) such as a previously unrecognised side effect or ADR related to a specific drug. It also helps to confirm a signal of an ADR with limited information from an alternative data source, such as the literature or post-marketing studies, and also in evaluating comparative risks of related drugs. Examples of some important early warnings of new ADRs identified since 1995 are provided in Table 2. In effect, when used within the known limitations of spontaneous reporting, principally under-reporting, the Yellow Card Scheme underpins the process of pharmacovigilance in the UK.

The initial objective and continuing purpose of the Yellow Card Scheme is to collect voluntary reports of ADRs to all licensed medicines, irrespective of legal status, and also those of unlicensed medicines including herbals. The MHRA also collects adverse incidents relating to medical devices since the MCA's merger with the MDA in April 2003, but these two reporting systems remain separate and continue to co-exist (section 3.15.3).

Reporting of ADRs related to medicines is entirely voluntary and therefore based on the goodwill of health professionals, although all those who prescribe medicines have, or should consider they have, a professional duty to report ADRs to the Scheme. As the reports are based on suspicions, no causal link needs to be established. Reporters are encouraged to report without delay so that unknown ADRs may be caught in the initial stages of marketing. Another principle established at the launch of the Scheme was that the data are never to be used for disciplinary purposes or for enquiries about prescribing costs (section 1.3.1; Annex C).

At present, the MHRA collates all ADRs associated with intensively monitored black triangle (▼) drugs and serious ADRs associated with older or more established drugs. Yellow Cards are sent directly to the MHRA or via the Regional Monitoring Centres (RMCs) (section 1.4.3). All reports are held in complete confidence by the MHRA and since the year 2000 Yellow Cards submitted by health professionals have been anonymised so that the identity of the patient is not revealed to the MHRA (section 1.4.6).

For linkage purposes health professionals provide a unique identifier, such as a local GP number, to enable the reporter to identify the patient and to provide follow-up data to the MHRA if such data are required. The MHRA has no means of linking the reporter's unique identifier to a particular patient, assuming the reporter has not included the patient's identifiable details.

Upon receipt of a Yellow Card the MHRA, as appropriate, requests additional information from the reporter when this is needed to clarify the significance of the ADR. Analysis of Yellow Cards is carried out 'in house' by MHRA staff and the MHRA is responsible for informing CSM and Ministers of any Yellow Card findings that impact on the safety of a licensed medicine.



## 1.3 HISTORY OF THE YELLOW CARD SCHEME

### 1.3.1 Initiation of the Yellow Card Scheme

Prior to the thalidomide disaster there was no formal drug regulation system in place to monitor the safety of medicines in the UK. In 1956, thalidomide was first marketed in West Germany as a sedative and hypnotic medicine; in April 1958 thalidomide reached the UK market under the trade name Distaval (Shah, 2001).

Thalidomide was strongly promoted by the manufacturer for the treatment of morning sickness during the early stages of pregnancy and was introduced into 46 countries world-wide between 1958 and 1960. The first cases of babies born with congenital malformation of the limbs, known as phocomelia, were reported in Germany in 1959. These congenital malformed limbs were also associated with other internal malformations.

When suspicions of a causal association with thalidomide were proposed to the manufacturer, the association was strongly refuted. However, the number of cases of phocomelia 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 (Shah, 2001). This was followed by its withdrawal from the majority of countries world-wide over the next nine months.

The thalidomide disaster highlighted the urgent necessity for a system of licensing and safety monitoring. In August 1962, the UK Government set up the Joint Sub-Committee of the English and Scottish Standing Medical Advisory Committee with Lord Cohen of Birkenhead as the Chairman. In their final report of March 1963 entitled 'Safety of Drugs', the Joint Sub-Committee proposed that a Committee on Safety of Drugs should be established with sub-committees to advise it on toxicity, clinical trials and therapeutic efficacy and adverse reactions (Ministry of Health, Scottish Home and Health Departments, 1963).

On 8 May 1963, The Right Hon Kenneth Robinson summed up the current climate in the UK when he commented in Parliament 'The house and the public suddenly woke up to the fact that any drug manufacturer could market any product, however inadequately tested, however dangerous, without having to satisfy any independent body as to its efficacy and safety and the public was almost uniquely unprotected in this respect.' (Penn, 1986).

This was followed by the establishment of the Committee on Safety of Drugs (CSD) in June 1963 by the Secretary of State for Scotland (The Right Hon William Ross), the Minister of Health (The Right Hon Kenneth Robinson) and the Minister of Health and Social Services, Northern Ireland (The Right Hon W J Morgan), in consultation with medical and pharmaceutical professionals and the Association of the British Pharmaceutical Industry (ABPI). Sir Derrick Dunlop was appointed as the first Chairman of the CSD.

On 4 May 1964, Sir Derrick circulated a letter to all doctors in the UK to inform them that the CSD was establishing a Register of Adverse Reactions to Drugs (Griffin and Webber, 1992; Annex C). A similar letter was circulated to dentists on 15 June 1964. This register was first proposed by Professor Leslie Witts.

In these letters Sir Derrick asked doctors and dentists ‘to report to us promptly details of any untoward condition in a patient which might be the result of drug treatment’ and to ‘complete it without delay’. He went on to confirm that ‘all the reports or replies that the Committee receive from doctors/dentists will be treated with complete professional confidence by the Committee and their staff. The Health Ministers have given an undertaking that the information supplied will never be used for disciplinary purposes or for enquiries about prescribing costs.’ These letters signalled the birth of the Yellow Card Scheme.

## **1.4 EXTENSIONS TO THE YELLOW CARD SCHEME**

### **1.4.1 The early days**

The UK spontaneous ADR reporting scheme soon became known as the Yellow Card Scheme as the reply-paid cards used by doctors and dentists to report ADRs were printed on yellow paper. Within the first year of use, up to 100 Yellow Cards were received by the CSD per week.

From the initiation of the Scheme, Sir Derrick made it clear that it was a voluntary scheme for ADRs, which meant that the reporter had considered a possible causal association between the medicinal product taken and the adverse reaction experienced by the patient, but had no need to prove causality.

The number of ADR reports received by year via the Yellow Card Scheme since 1964 are provided at Annex G. The Scheme has developed over the years through several reporting initiatives of the MHRA and CSM in addition to other outside influences. In the mid-1970s, ADR reporting increased following the withdrawal of practolol and its associated oculomucocutaneous syndrome, the introduction of the CSM drug safety bulletin *Current Problems in Pharmacovigilance*, and the inclusion of a yellow page in GP prescription pads reminding GPs to report ADRs.

In 1986, a further increase in Yellow Card reports followed the inclusion of the Yellow Card in GP prescription pads and the British National Formulary (BNF). In the early 1990s ADR reporting decreased, possibly as a consequence of increasing time demands upon GPs (Davis and Raine, 2002). In 2000 a substantial increase in ADR reporting was associated with the meningitis C vaccination campaign for all children in the UK under the age of 18 years.

Even in the early days the CSD identified areas for improvement, including the introduction of a list of drugs that required intensive monitoring, providing feedback to reporters through drug safety bulletins and collating information on patient exposure.

A computer system for storing ADR reports was initiated in 1967, and the first confidential feed-back was provided to doctors and dentists who contributed to the Scheme. In the same year, the CSD became involved in the World Health Organization (WHO)'s Pilot Study on the Monitoring of Adverse Reactions to Drugs.

The CSD was replaced by the Committee on Safety of Medicines (CSM) which first met on 25 June 1970 under the Chairmanship of Professor E F Scowen. CSM revised the Yellow Card in 1971 to request more information than on the original version and to stimulate reporting of ADRs. This proved to be a success which encouraged further enhancements of the Scheme.

In January 1976, the Black Triangle (▼) Scheme was introduced to highlight certain medicines for which intensive monitoring was required. These medicines were identified by the inclusion of an inverted black triangle symbol (▼) on the product information. Under a voluntary agreement with pharmaceutical companies, all new drugs, established drugs with new indications or routes of administration and new combination products of established drugs, carry this symbol adjacent to the product name on all their literature. The Black Triangle (▼) Scheme is still in operation today.

#### **1.4.2 Working Party on Adverse Reactions**

The Working Party on Adverse Reactions was established in 1983 following the removal from the market of the non-steroidal anti-inflammatory drug Opren (benoxaprofen) in the UK.

In the same year, a review of the Yellow Card Scheme was conducted by the Working Party on Adverse Reactions under the chairmanship of Professor D G Grahame Smith (Annex J). The terms of reference of the Working Party on Adverse Reactions were 'to consider how best the Committee on Safety of Medicines should fulfil its statutory functions of promoting the collection and investigation of information relating to adverse reactions, for the purpose of enabling it to give advice on safety, quality or efficacy of medicinal products; and to make recommendations.'

The Working Party reviewed the Yellow Card Scheme and made 29 recommendations to stimulate ADR reporting (Annex J). Included within their recommendations they:

- advised that medical schools should be encouraged to review the arrangements for training students about the importance of drug histories and ADRs, and the need to report;

- proposed that revised advice should be issued to doctors on the kinds of adverse reactions the CSM wished them to report;
- suggested that further consideration should be given to attaching a Yellow Card or a reminder about reporting to the FP10 prescription pad;
- proposed that further consideration should be given to the role of hospital pharmacists in assisting doctors in reporting ADRs;
- did not consider that it would be helpful to offer doctors payment for reporting;
- did not consider that reporting should be a statutory requirement;
- advised that CSM should maintain its policy of not accepting reports directly from patients.

The Working Party also recognised that any amendment to the Yellow Card Scheme should have a positive influence on the quality of the reports collated, and proposed that doctors should be contacted via publications and medical journals advising them of the kinds of ADRs that CSM would like them to report.

In July 1985 the Working Party on Adverse Reactions reconvened with the remit to review the progress since the first report was approved by Ministers in 1984, and to consider how the CSM post-marketing surveillance system could be developed. A second report with 13 recommendations included the proposal that post-marketing surveillance studies should be considered on a voluntary basis by pharmaceutical companies in association with the CSM (Annex K).

### **1.4.3 Regional Monitoring Centres (RMCs)**

In the 1980s, hospital-based CSM Regional Monitoring Centres (RMCs) were established for the West Midlands, Northern, Wales and Mersey regions to strengthen local reporting and encourage participation by providing feedback to health professionals in their regions (Houghton *et al*, 1996; Davis and Raine, 2002).

A fifth RMC was opened in Scotland in October 2002 and the Northern RMC expanded its activities into Yorkshire in September of the same year. Research performed by the RMCs has demonstrated the value and feasibility of extending the Scheme to other reporter groups including hospital and community pharmacists and nurses and, more recently, in the introduction of the electronic Yellow Card resulting in important enhancements of the Scheme (sections 1.4.5 and 1.4.7). Local awareness of the RMCs is high with increased reporting rates in areas served by RMCs compared with elsewhere. Recent evidence from Scotland and Yorkshire has shown increases in reporting following the establishment of RMC support in these areas.

This increase in report numbers is not at the expense of a reduction in the quality or relevance of reports since the proportion of reports involving black triangle (▼) drugs or serious reactions is at least as high as for non-RMC areas. RMCs follow up Yellow Card reports according to standard operating procedures set out by the MHRA. RMCs request follow-up information on proportionately fewer reports than the MHRA – perhaps because reports to them are more often completed – and their rates of success in follow-up are high.

There are several reasons for the RMCs' success. All the RMC directors are clinical pharmacologists with commitments to acute general medicine, and they and their pharmacists provide expert advice to their clinical colleagues in their own regions. The Centres liaise or are integrated with Regional Drug Information services, further improving professional communication.

RMCs are also an important focus for education in pharmacovigilance and drug safety for undergraduates and postgraduates in medicine, pharmacy and nursing in their own regions and nationally. At least part of the reason for the increased reporting rates arising from RMC areas appears to be the delivery of education to targeted reporter groups locally. Use of data on local patterns of reporting is essential to this process. RMCs have helped ensure that syllabuses and examinations for health professionals, including supplementary prescriber groups, contain the appropriate reporting of ADRs.

The clinical expertise that RMCs provide extends to regional and national committees, including the CSM and its Sub-Committee on Pharmacovigilance (SCOP); many current and previous members of these committees have been trained in RMCs. Postgraduate training and experience in pharmacovigilance could not be delivered by the MHRA in a clinical setting and it is essential that the ability of RMCs to provide this training is not compromised.

#### **1.4.4 Special reporting schemes**

In order to improve reporting of ADRs via the Scheme, Yellow Cards were added to GP prescription pads in 1986, to the copies of the British National Formulary (BNF) and the Monthly Index of Medical Specialities (MIMS). The success of the addition of the Yellow Card to GP prescription pads was evident through the large rise in spontaneous ADR reporting (Annex G).

Over the years, the Yellow Card Scheme has been promoted via articles in medical and pharmaceutical journals, and promotional packs have been provided to new reporters to the Scheme. In order to encourage reporting in specific patient groups, special schemes were launched which included adverse reactions to herbal products and HIV drugs and a pilot scheme to stimulate reporting of ADRs in children.

### (i) Unlicensed herbal products

In October 1996, the Yellow Card Scheme was extended to include reporting of ADRs to unlicensed herbal remedies. This extension to the Scheme followed the report of potentially serious reactions associated with unlicensed herbal remedies reported in Guy's Hospital Toxicology Unit (Anon, 1996; Shaw *et al*, 1996). These included nine cases of toxicity from heavy metals following exposure to traditional remedies from the Indian sub-continent and 21 cases of hepatic toxicity, two of which were fatal, associated with the use of traditional Chinese remedies. Prior to this, the Yellow Card Scheme only collected ADRs to licensed herbal products; in 1995 less than 0.2% of all ADR reports were associated with these products (Davis and Raine, 2002).

Following initiation of the Scheme, there was a two-fold increase in the levels of reporting of ADRs associated with herbal remedies between 1998 (40 reports received) and 2001 (over 70 reports received). The influx of ADR reports to unlicensed herbal products soon proved to be a valuable source of data for the evaluation of drug interactions between St John's Wort (*Hypericum perforatum*) and other drugs, including the oral contraceptive pill (Anon, 2000a).

### (ii) HIV reporting scheme

In the mid-1990s, a number of the new anti-Human Immunodeficiency Virus (HIV) drugs were introduced. These were tested in a relatively small number of patients during clinical trials and therefore the side effect profile of these drugs was limited at the time of licensing (Davis and Raine, 2002). Reporting of ADRs to these medications by specialised physicians was low, and concern arose that the complexity of anti-HIV drug regimens through their co-administration and potential interactions was acting as a deterrent to reporting in this patient group.

In order to increase the reporting of ADRs associated with anti-retroviral therapies, the HIV Adverse Drug Reactions Reporting Scheme<sup>6</sup> was launched in November 1997 as a collaboration between the MHRA, the CSM and the Medical Research Council HIV Clinical Trials Centre (Anon, 1998a). Specialist health professionals, which included doctors, nurses and pharmacists, were requested to report ADRs in HIV patients on special reporting forms which did not require identifiable details of the patient, as confidentiality was seen as another major deterrent for not reporting ADRs in this patient group.

The success of the Scheme was soon apparent and within the first seven months following its launch, 207 reports were submitted compared to 112 reports collected by the MHRA and CSM during the seven months prior to the launch of the Scheme (Anon, 1998b).

---

<sup>6</sup> <http://medicines.mhra.gov.uk/ourwork/monitorsafequalmed/adrschemes/hivadrscheme.htm>

The ADRs collected through this Scheme were analysed regularly and data were fed back to reporters via the newsletter *HIV ADR Reporting Scheme News*<sup>7</sup>.

### (iii) Paediatric pharmacovigilance initiatives

In the late 1990s there was increasing concern over the use of drugs in children outside their licensed indications ('off label' usage) together with a dearth of clinical trials in children. The MHRA recognised the importance of collecting ADR data, particularly within this patient population, as the ADR profile of particular medicines may differ significantly in children. In 1997 and 1998, it is estimated that only 8% of the ADR reports received by the MHRA and CSM were in children less than 18 years of age (Davis and Raine, 2002).

In September 1998, a pilot Paediatric Regional Monitoring Centre (PRMC) was established in the Trent region to stimulate paediatric ADR reporting, targeted at paediatricians and hospital pharmacists. A monthly reminder letter and presentations to staff in the identified hospitals were made as proactive interventions.

An analysis, completed two years following the initiation of the Scheme, demonstrated an increase in absolute numbers of ADRs in children received by the MHRA from the Trent region, with the majority of reports relating to the meningitis C vaccine which had coincided with the nation-wide vaccination campaign (Davis and Raine, 2002).

In 2000, the CSM set up a Paediatric Working Group to advise on improving the availability of licensed medicines for children and to seek ways of improving reporting of ADRs in children. This included a pilot study using the 'Orange Card' reporting scheme operated by the British Paediatric Surveillance Unit (BPSU), part of the Royal College of Paediatrics and Child Health, in conjunction with the MHRA.

## 1.4.5 Reporters to the Yellow Card Scheme

When the Yellow Card Scheme was initiated in 1964, doctors and dentists were the only designated reporters under the terms of the Scheme (section 1.3.1). In 1969 the Scheme was extended to include coroners as reporters (Shah, 2001).

### (i) Independent and supplementary prescribing, patient group directions (PGDs)

In the last two decades, the roles of nurses and pharmacists have been changing through independent prescribing, supplementary prescribing and patient group directions (PGDs).

---

<sup>7</sup> <http://medicines.mhra.gov.uk/ourwork/monitorsafequalmed/adrschemes/hivadnews.htm>

Independent prescribers take responsibility for the clinical assessment of the patient, establish a diagnosis and the clinical management required, and are responsible for prescribing where necessary and the appropriateness of any prescription<sup>8</sup>. After the Crown Reports in the late 1990s<sup>9</sup>, nurses with a district nurse or health visitor qualification have been able to train to prescribe independently from a limited formulary of products (the Nurse Prescribers' Formulary for District Nurses and Health Visitors) consisting of appliances, dressings and some medicines, including a small number of prescription only medicines (POMs). The training for prescribing from this Formulary is now incorporated into the basic training of all new district nurses and health visitors. Details of the formulary are set out in both the British National Formulary (BNF) and Part XVIIB(i) of the Drug Tariff.

In addition, all first level registered nurses and registered midwives may now train to prescribe independently from the Nurse Prescribers' Extended Formulary (NPEF). The Extended Formulary includes all licensed pharmacy (P) medicines and all general sales list (GSL) medicines which can be prescribed at NHS expense (this excludes controlled drugs with the exception of lower strength P and GSL medicines containing codeine phosphate and dihydrocodeine tartrate) and a range of almost 180 POMs to treat a list of specified medical conditions. Nurses should not prescribe for conditions that are outside this list. Details of the NPEF are available in both the BNF and Part XVIIB(ii) of the Drug Tariff.

Amendments to NHS Regulations enabled the introduction of supplementary prescribing for nurses, midwives and pharmacists from April 2003<sup>10</sup>. Supplementary prescribing is a voluntary prescribing partnership between an independent prescriber and a supplementary prescriber to implement an agreed patient-specific clinical management plan with the patient's agreement. Agreement to the plan has to be recorded by both the independent prescriber (doctor or dentist), the supplementary prescriber and the patient before supplementary prescribing begins.

Unlike independent nurse prescribing, there is no specific formulary or list of medicines for supplementary prescribing. The prescribing of medicines is allowed provided they are referred to in the patient's clinical management plan. This applies to all POM medicines, P medicines, GSL medicines, appliances and devices, foods and other borderline substances approved by the Advisory Committee on Borderline Substances (ACBS), with the current exception of controlled drugs.

---

8 Mechanisms for Nurse and Pharmacist Prescribing and Supply of Medicines  
<http://www.dh.gov.uk/assetRoot/04/06/99/06/04069906.pdf>

9 Review of prescribing, supply and administration of medicines: *A report on the supply and administration of medicines under group protocols* (Department of Health, London, April 1998); Review of prescribing, supply and administration of medicines, final report. (Department of Health, London, March 1999).

10 <http://www.dh.gov.uk/PolicyAndGuidance/MedicinesPharmacyAndIndustryServices/Prescriptions/SupplementaryPrescribing/fs/en>



However, subject to Parliamentary approval to changes to the Home Office's Misuse of Drugs Regulations and to related amendments to NHS Regulations, it is anticipated that nurses and pharmacists will be able to prescribe controlled drugs under a supplementary prescribing arrangement later in 2004.

Supplementary prescribers are also able to prescribe medicines for use outside of their licensed indications (ie 'off label' prescribing), black triangle (▼) drugs, drugs marked 'less suitable for prescribing' in the BNF and unlicensed drugs that are part of a clinical trial which has a clinical trial certificate or exemption. There are no legal restrictions on the clinical conditions which supplementary prescribers may treat. It is for the independent prescriber to decide, prior to drawing up the clinical management plan with the supplementary prescriber, whether supplementary prescribing will be appropriate.

Training for supplementary prescribing for nurses is the same as for extended formulary nurse prescribing, with the addition of a short module covering the context and concept of supplementary prescribing. Nurses who are eligible to train to prescribe from the NPEF are also able to train as supplementary prescribers. Nearly 2,000 nurses are qualified and registered with the Nursing and Midwifery Council to prescribe from the NPEF, of whom over 1,300 have also qualified as supplementary prescribers.

Pharmacists began training as supplementary prescribers in September 2003, and nearly 30 pharmacist supplementary prescribers have now been registered with the Royal Pharmaceutical Society. The Department of Health and the MHRA will shortly be consulting on proposals to extend supplementary prescribing to additional health professionals.

Another new method of supplying and administering medicines is through patient group directions (PGDs)<sup>11</sup>. Pharmacists, nurses, midwives, health visitors, optometrists, chiropodists, radiographers, orthoptists, physiotherapists and ambulance paramedics are allowed to use PGDs.

PGDs are documents which permit medicines to be legally supplied or administered to groups of patients who may not be individually identified before presentation for treatment. This means, for example, that in hospitals, nurses may be authorised to supply certain medicines to defined groups of patients without reference back to doctors. Similarly, in the community, practice nurses may be allowed by their employing GPs to give courses of immunisations to babies and young children without individual authorisation on every occasion.

---

11 Health Service Circular 2000/026 Patient Group Directions [England Only]

**(ii) Pharmacist reporting**

When the CSM considered opening the Yellow Card Scheme to pharmacist reporting, pharmacists were already recognised reporters in a number of other countries besides the UK (Griffin, 1986). Pilot studies of ADR reporting by hospital pharmacists were conducted in 1984 (Winstanley *et al*, 1989) and 1992 (Lee *et al*, 1997).

In April 1997, the Yellow Card Scheme was extended to include hospital pharmacists as recognised reporters of ADRs (Anon, 1997a). An evaluation of the ADR reports received from hospital pharmacists during the first year of reporting revealed their ability to report effectively and to a similar standard as hospital doctors, in addition to providing supplementary reports to those received from the doctors (Davis *et al*, 1999).

The Yellow Card Scheme was extended again to include nation-wide reporting of ADRs by community pharmacists from November 1999 (Anon, 1999). This followed a successful pilot scheme for community pharmacist reporting by the RMCs, which demonstrated that reports received from community pharmacists were of a comparable standard to those submitted by GPs.

With the expanding range of over-the-counter (OTC) medicines, the contribution of pharmacists to the Yellow Card Scheme has become increasingly important and pharmacists' contribution will grow with the increasing number of medicines whose legal status has changed. The responsibility of providing guidance to patients on the safe use of medicines will more frequently fall to the pharmacist. Their expanding role as prescribers means they are well placed to report ADRs via the Scheme.

In 2004, hospital and community pharmacists continue to contribute substantially to the Yellow Card Scheme. In the fiscal year of 2002/2003, 15% of all ADR reports originated from hospital pharmacists and a further 3% were from community pharmacists (MCA Annual Report 2002/2003).

**(iii) Nurse reporting**

In the late 1990s, nurses increased their involvement in the routine care of patients through the prescription of a limited number of medicines and were therefore in a position to report ADRs in patients who were under their care.

In November 1999 during the meningitis C vaccination campaign, nurses began to submit ADR reports to the MHRA. At this stage nurses were not recognised reporters to the Yellow Card Scheme, but CSM recognised their valuable contribution and accepted that they could be reporters for the duration of the meningitis C vaccination campaign. In addition, a pilot scheme to investigate nurse reporting was conducted by the RMC in Merseyside (Morrison-Griffiths, 2000).

An evaluation of the meningitis C vaccine Yellow Cards submitted by nurses and the pilot scheme, demonstrated that nurses reported similar proportions of serious ADRs as other recognised reporters and that, with appropriate training, nurses could be important contributors to the Yellow Card Scheme. As a result, the Scheme was extended to all nurses, midwives and health visitors in October 2002. A recent analysis of the role of community and hospital nurses in reporting of ADRs demonstrated that the proportion and quality of reports received from nurses were similar to those received from doctors (Morrison-Griffiths *et al*, 2003).

#### (iv) Patient reporting via NHS Direct

Since the 1983 Review chaired by Professor Grahame Smith, there has been ongoing debate about the role of the patient in submitting reports direct to the Yellow Card Scheme. In April 2003, patient reporting ‘in partnership’ was launched via a pilot reporting scheme in South East London through NHS Direct. Staff at the NHS Direct call centre make the reports on behalf of patients, in fulfilment of a pledge given in October 2002 by Ministers. The Scheme is to date restricted to the NHS Direct call centre in Beckenham.

By the end of March 2004, 39 reports had been received from NHS Direct South East London by the MHRA and CSM as a result of this initiative. These data are under continuous review but, in general, the pilot scheme has not been successful. In addition, it has been criticised by some stakeholders for not collecting the patient perspective directly from the patients themselves.

#### 1.4.6 ‘Anonymisation’ of the Yellow Card

In September 2000, the Yellow Card was updated in line with the Data Protection Act 1998<sup>12</sup> and with the General Medical Council (GMC) guidelines on confidentiality (General Medical Council, 2000)<sup>13</sup>. Prior to this, reporters were asked for the patient’s name and date of birth in order to facilitate follow-up of Yellow Card reports for additional data and to identify duplicate reports.

The new Data Protection legislation required that personal information should not be disclosed without the consent of the individual concerned. Although there were exceptions to this requirement, including where the data are in the public interest eg to protect public health, the MHRA/CSM updated the Yellow Card to remove personal identifiers.

The Yellow Card was ‘anonymised’ so that name and date of birth are no longer required (Anon, 2000b; Anon, 2000c). Instead, the initials and age of the patient are requested,

---

12 <http://www.hmsa.gov.uk/acts/acts1998/19980029.htm>

13 The GMC Guidelines were updated in April 2004 ‘Confidentiality: Protecting and Providing Information’. <http://www.gmc-uk.org/standards/secret.htm>

along with a local identifier for the patient such as a practice or hospital number. The inclusion of this identification number enables the patient to be identifiable to the reporter but not to the MHRA and CSM, and allows for follow up. In this way, the Yellow Card satisfies the requirements of the Data Protection Act 1998 and the GMC guidelines on patient confidentiality.

A number of other minor changes were also introduced to the Yellow Card to help alert reporters to the types of reaction in which the MHRA and CSM were particularly interested, and to ask reporters for their interpretation of the seriousness of the ADR.

Five months after the introduction of the anonymised Yellow Card, comparative analysis of 200 old Yellow Cards and 200 updated Yellow Cards revealed that the areas of concern, namely the number of reports received, the success of follow up, duplicate and invalid reports, had not been adversely affected by anonymisation.

#### **1.4.7 Information technology and electronic reporting**

In 1978, the computer system used to record the data collated via the Yellow Card Scheme was updated to facilitate regular analyses and enquiries. This was later replaced by the Adverse Drug Reactions On-line Information Tracking (ADROIT) database which was introduced in 1991 to hold data on both UK and foreign ADR reports.

ADROIT holds the Yellow Card data in two formats. The scanned images of Yellow Cards are in an unstructured format while details of the report, which are entered onto the database by staff at the MHRA, are in a structured format. Following anonymisation of the Yellow Card (section 1.4.6), patient names were removed from the structured data on the database and replaced by initials. However, the data held in an unstructured format were not amended.

In addition to updating the way in which the data are stored, there have also been advances in the way the data are received from reporters. With recent advances in information technology, the MHRA and CSM recognised that the paper Yellow Card may no longer be the most convenient method of reporting. This was compounded by the acknowledgement that one of the main reasons why health professionals do not report ADRs is through lack of time (Bateman *et al*, 1992; Belton *et al*, 1995; Sweis and Wong, 2000).

In 1995 a small number of pharmaceutical companies began to submit their ADR reports electronically via the ADROIT Electronically Generated Information Service (AEGIS). A pilot scheme was later introduced in 1998 for health professionals to submit their Yellow Cards electronically, with the assistance of GP systems suppliers EMIS and AAH Meditel (Anon, 1997b). This meant that GPs could automatically transfer patient details and drug information from the patient's computerised records to the electronic Yellow Card.

In response to requests from health professionals for an internet-based reporting facility, CSM convened an Electronic Reporting Working Group in 2002. The electronic Yellow Card was launched in October 2002 on the MHRA website<sup>14</sup>. This electronic Yellow Card enables reporters to continue to report ADRs without completing and posting the paper version and although it is still in its infancy, 274 Yellow Cards were received via the internet by the MHRA and CSM in the first year of use. Feedback from reporters who use the electronic Yellow Card is under close review by the MHRA.

## **1.5 EUDRAVIGILANCE**

EudraVigilance is the European data-processing network and database management system for the exchange, processing and evaluation of Individual Case Safety Reports (ICSRs) related to medicinal products authorised in the European Economic Area (EEA). Over the last decade, EU Competent Authorities, the European Agency for the Evaluation of Medicinal Products (EMA) and the European Commission have been working towards the creation of a central pharmacovigilance database supported by a system of mandatory electronic ADR reporting between the pharmaceutical industry and the regulators.

The reporting requirements of the MHRA are set down in Council Regulation (EEC) 2309/93 for products authorised by the centrally-authorised procedures, and by Commission Directive 2000/38/EC for products authorised by national licensing procedures which include the Mutual Recognition system. Specifically, the MHRA is required to send details of all serious<sup>15</sup> UK ADR reports it receives from any health professional or pharmaceutical company to the EudraVigilance database within 15 days of receiving the report.

The system became operational on 5 December 2001 and has continued to be developed since that date, although the majority of Member States and pharmaceutical companies are not yet in a position to begin electronically reporting to EudraVigilance.

Once all Member States and pharmaceutical companies are able to submit electronic reports to EudraVigilance and the backlog issues have been resolved, the EMA will, in principle, hold a complete record of all reported serious adverse reactions in the EU and all serious, unexpected reactions from outside the EU if an EU-marketed drug is implicated.

EudraVigilance includes a standard query tool to allow the searching and retrieval of information from the database. The European Commission, EMA and EU Competent Authorities will have full access to the EudraVigilance database via a secure internet connection. The pharmaceutical industry will have access to a limited data-set comprising

---

14 <http://www.yellowcard.gov.uk>

15 Based on the Council for International Organizations of Medical Sciences (CIOMS) criteria of 'serious'

reports which they themselves have submitted to EudraVigilance or have been submitted via the Competent Authorities. There is no access for the public at present.

The EMEA has requested that all reports received after 1 January 1995 are retrospectively submitted to the EudraVigilance system. There is considerable debate within Member States about whether competent authorities or the pharmaceutical industry should supply this information.

The MHRA's preliminary position is that UK data would be best submitted by the MHRA as they hold the only complete data source for UK reports and the issue of duplicate reports has already been addressed in the ADROIT system, but a policy decision remains to be made.

In the interim, until electronic submission is feasible, the MHRA only reports serious UK adverse reactions for centrally authorised products to the EMEA. This is achieved by way of a fortnightly Excel line-listing which will continue until the MHRA is fully technically compliant. This line-listing contains no patient or reporter identifiable data (data fields submitted are: MHRA identification number, company identification number, country, source (eg nurse), patient age and sex, suspect drug, dose, duration of treatment, reaction and outcome).

In future, with full electronic reporting, the information sent to the EMEA could be more comprehensive both at the aggregated and at the individual report level. With regard to confidential data, a valid electronic report must contain one of the following fields to identify a reporter: family name, organisation, postcode, country, qualification, literature reference or study name.

A final policy decision remains to be made by the MHRA but it is currently proposed to send only country and qualification of the reporter. Similarly, at least one field from the following list must be used to identify a patient: initials, GP number, specialist number, hospital number, birth date, age, age group or sex. Again, a final policy decision remains to be made but it is proposed to send only age group and sex. By taking this approach, the MHRA should avoid any issues of personal data confidentiality.

## 2 METHODOLOGY

### 2.1 STEERING COMMITTEE FOR THE REVIEW

The Terms of Reference announced by Lord Warner on 21 July 2003 described the scope of the Review and that it would be headed by Dr Jeremy Metters, former Deputy Chief Medical Officer at the Department of Health, Annex D. The methodology for the Review was left open.

As the Review was to be wide-ranging in its coverage of public health, scientific, ethics, genetic, data protection, legal and other aspects of the Yellow Card Scheme and database, Dr Metters recommended that a small multidisciplinary Steering Committee should be convened. This proposal was welcomed by Sir Alasdair Breckenridge (Chairman of the MHRA). Experts knowledgeable in the disciplines directly relevant to the Review were invited to join the Steering Committee. A list of the members of the Steering Committee is at Annex B.

Membership was planned to take particular account of the complex and perhaps conflicting issues of confidentiality of personal health data, ethics, genetic susceptibility and data protection. With the exception of the Chairman of the CSM, whose appointment was in his ex officio capacity, the Committee members were invited to serve on the basis of their personal expertise and knowledge and not as representatives of any institution, body or interest group.

The task of the Committee was to carry through the Review, analyse the responses to the stakeholder consultation and develop conclusions and recommendations that have broad stakeholder support. The MHRA provided the secretariat for the Review.

#### 2.1.1 Timetable

As the Terms of Reference specifically referred to the identification of stakeholders and their interests, it was also agreed that a period for consultation with stakeholders was essential. For this reason, the initial requirement for the Review to be completed during 2003 was set aside.

### 2.1.2 Steering Committee meetings

The papers for the first Steering Committee meeting (29 September 2003) included the history of the Yellow Card Scheme, the background to the Review, the remit of the Committee and agreement on the terms of the public consultation. The Steering Committee agreed that their procedures should be as open as possible and that the agreed minutes of this and all subsequent Steering Committee meetings (Annex L) should be placed on the MHRA website<sup>16</sup> during the Review.

At the second meeting (1 December 2003) the Steering Committee discussed the ADROIT database, the General Practice Research Database (GPRD), EudraVigilance and issues related to the Review, including ethical issues in genetics; ethics and data protection; audit, governance and devolved issues; pharmacy and patient perspectives; reporter perspectives; public health and operational impact.

At the third meeting (12 January 2004) which followed the end of the consultation period (9 January 2004), the Steering Committee was updated on the responses to the consultation, key stakeholder meetings and legal issues (FOI and the Data Protection Act 1998) related to release of Yellow Card data. Initial views on the issues raised by the Review were explored.

At the fourth meeting (16 February 2004) the Steering Committee considered unique comments from stakeholders and discussed their main conclusions and recommendations to date.

The Review report was finalised at the fifth meeting (26 March 2004), subject to minor amendments agreed through correspondence.

## 2.2 CONSULTATION EXERCISE

Opening access to the Yellow Card Scheme raises issues of public health, ethics, research, controls on use of Yellow Card data, conditions on access, legal issues, operational impact and confidentiality. Multiple stakeholders were identified, including health professionals (reporters), patients, the pharmaceutical industry, the research community, the Licensing Authority and wider Government, the EMEA and the general public.

On 6 October 2003, Dr Metters, on behalf of the Steering Committee, initiated a 12-week public consultation reviewing access to Yellow Card data.

A consultation letter was circulated within the health services to interested organisations and officials in the Scottish Executive, Welsh Assembly and Northern Ireland (devolved administrations), and other organisations and individuals who had an interest in the

---

<sup>16</sup> [http://medicines.mhra.gov.uk/ourwork/monitorsafeequalmed/yellowcard/review\\_membership.htm#minutes](http://medicines.mhra.gov.uk/ourwork/monitorsafeequalmed/yellowcard/review_membership.htm#minutes)



collection and analysis of data on ADRs via the Yellow Card Scheme, and the potential implications for releasing these data, Annexes E with H.

The letter explained that the primary purpose of the Review was to consider whether, and if so under what conditions and for what purposes, the data should be made more widely available. Comments were requested by 9 January 2004. The consultation letter was also placed on the MHRA website<sup>17</sup>.

In addition to the public consultation exercise, a number of key stakeholders were identified as having a specific interest in the Review. They were invited to present their views orally as well as in writing on the issues raised by the Review directly to the Steering Committee (Annex F). These meetings and the responses to the consultation were used to inform the report of the Review.

### 2.2.1 Responses to the consultation

A total of 55 responses to the consultation were received by the MHRA secretariat on behalf of the Steering Committee. These can be broadly categorised into different groups by organisation type (Table 3), and a table summarising the consultation responses is provided below (Table 4). A synopsis of the main issues raised in each response was considered and analysed. All responses to the consultation exercise are provided at Annex I.

**Table 3 Broad categorisation of consultation responses**

<i>Organisation type</i>	<i>No. of responses</i>
Royal Colleges	5
Pharmacy interest	4
Medical interest	6
Academia/researchers	6
Committees	7
Industry	4
Devolved administrations/Government	4
Other bodies	18
No comment	1
<b>Total:</b>	<b>55</b>

## 2.3 THE REPORT

Chapter 3 describes the Steering Committee's analysis of the views and responses from stakeholders on which the Committee's conclusions and recommendations are based.

<sup>17</sup> <http://www.mhra.gov.uk/news/2003/yellowcardconsultation.doc>

**Table 4 Summary of consultation responses in order received by the Steering Committee**

	Should aggregated data be available for audit management purposes	Should aggregated data be available for financial gain	Should patients be able to report directly to the Scheme	Should there be a charge for access to the data for research purposes	Should a fee be paid to the reporter/GP if further information is required for research purposes	Should there be an independent ethics committee to evaluate research proposals	Should genetic research be permitted	Should data be made available for research purposes	Should patients be able to report directly to the Scheme	Should there be a charge for access to the data for research purposes	Should a fee be paid to the reporter/GP if further information is required for research purposes
National Institute for Clinical Excellence											
British Heart Foundation	✓		✓								
Association of Chief Police Officers in Scotland											
Dr Herxheimer and Mr Medawar	✓		✓	✓	✗	✓					
Scottish Specialists in Pharmaceutical Public Health	✓	✓	✓			✓	✓	✓			
Dr Bateman (SCOP member, RMC head)	✓		✓	✓							
Dr Thompson	✓										
National Public Health Service for Wales		✓	✓		✗	✗				✓	
The Co-operative Pharmacy Technical Panel	✓										
Royal College of General Practitioners (RCGP)	✓	✓	✓	✗				✓	✓	✓	
Insulin Dependent Diabetes Trust	✓	✓	✗	✗	✓	✓	✓	✓	✓	✓	
Dr Waller	✓	✓	✓	✗		✓		✓	✓	✓	
North West Medicines Information Centre	✓	✓	✓		✗	✓		✓	✓	✓	
Medicines Commission	✓	✓	✓	✗	✗				✓	✓	
Association for Nurse Prescribing	✓	✓	✓	✗				✓	✓	✓	
Royal College of Nursing											
GSK	✓	✓	✓		✗	✗				✓	
National Patient Safety Agency	✓				✗					✓	
Novartis	✓	✓								✓	
CSM Scotland	✓	✓	✓	✗							
British Pharmacological Society	✓	✓	✓	✓	✗			✓			
Scottish Medicines Consortium	✓	✓	✓		✗			✗			
Drug Safety Research Unit	✓	✓	✓								
Royal College of Physicians (Edinburgh)	✓	✓	✓	✗				✓		✓	✓
Dr Taylor	✓	✓	✓	✗				✓	✓	✓	✓
Health Professions Wales	✓		✓	✗	✗					✓	
Professor Hunt (SCOP member)	✓	✓	✓		✗	✓				✓	
Dr Beard (SCOP member)		✓			✗					✓	
Professor Pirmohamed (SCOP member, RMC head)		✓	✓		✗	✗	✓	✗			
Royal College of Physicians (London)	✓	✓	✓		✗	✓				✓	
Faculty of Pharmaceutical medicine	✓	✓	✓		✗	✓				✓	

✓ = positive response, ✗ = negative response

**Table 4 Summary of consultation responses in order received by the Steering Committee (continued)**

	Should aggregated data be available for audit management purposes	Should aggregated data be available for financial gain	Should patients be able to report directly to the Scheme	Should there be a charge for access to the data for research purposes	Should a fee be paid to the reporter/GP if further information is required for research purposes	Should patients be able to report directly to the Scheme and reporters	Should there be an independent ethics committee to evaluate research proposals	Should access to Yellow Card data be more widely available	Should there be an independent ethics committee to evaluate research proposals	Should access to Yellow Card data be more widely available
Guild of Healthcare Pharmacists	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ARC Epidemiology Unit	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
British Medical Association	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Medical Women's Federation	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Dr Lott	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Mind	✓	✓	✓	✓	✓	✓	✓	✓	✗ (publicly funded)	✗
Professor McKeigue (LSHTM)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Welsh Assembly	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓
Association of the British Pharmaceutical Industry	✓	✓	✓	✓	✗	✓ (This is unavoidable)	✓	✓	✓	✓
Johnson & Johnson	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Royal Pharmaceutical Society of Great Britain	✓	✓	✓	✓	✓	✓ (This is unavoidable)	✓	✓	✓	✓
Scottish Consumer Council	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Department of Health and MRC	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Association of Respiratory Nurse Specialists	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓
Professor Troop (Health Protection Agency)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Consumers' Association	✓	✓	✗	✓	✗	✓	✓	✓	✓	✓
Dr Miller (Health Protection Agency)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Professor Evans (LSHTM)	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓
The Wellcome Trust	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Chief Scientist's Office, Scottish Executive	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Department of Health, Social Services and Public Safety (Northern Ireland)	✓	✓	✓	✓	✗	✗	✓	✓	✓	✓
Professor Langman (JCVI)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Professor Mann	✓	✗	✓	✓	✗	✗	✓	✓	✓	✓
Eastern Health & Social Services Council (Northern Ireland)	✓	✓	✗	✓	✓	✓	✓	✓	✓	✓
Total: ✓	45	36	8	33	3	3	14	10	25	6
Total: ✗	1	1	3	2	13	23	3	2	1	1
Total: No Comment	9	18	44	20	39	29	38	43	29	48
<b>Total</b>	<b>55</b>	<b>55</b>	<b>55</b>	<b>55</b>	<b>55</b>	<b>55</b>	<b>55</b>	<b>55</b>	<b>55</b>	<b>55</b>

✓ = positive response, ✗ = negative response

# 3 CONSULTATION ISSUES

## 3.1 PUBLIC HEALTH

Two important principles, which are the foundations for the recommendations in this report, emerged during the consultation. First and foremost, all stakeholders emphasised **the value and importance of the Yellow Card Scheme for public health and for the benefit of patients**. Secondly, stakeholders will not support **any changes that might harm the Scheme or deter reporters from submitting Yellow Cards to the Scheme**.

*‘Yellow Card data is a unique resource of invaluable information, collected over a drug’s marketing lifetime.’ British Pharmacological Society (Annex I).*

*‘Nothing should be done which might erode the confidence of doctors who form the only group capable of diagnosing, investigating and treating adverse drug reactions. Other groups can contribute greatly but the place of doctors in this process is vastly important and this fact needs to be recognised.’ Professor Ronald Mann (Annex I).*

The Steering Committee recommends **that the basic principles of the Scheme, as set out in Sir Derrick Dunlop’s letters in 1964, should not be changed. Any new uses of Yellow Card data should strengthen the Scheme but must not put its future at risk.**

The interested parties who are likely to request access to the Yellow Card data are researchers and academics, health professionals, the pharmaceutical industry, other regulatory authorities, the Government, NHS Trusts, and the media. Most requests would be for subsets of the data but a few could be for access to the entire database to research signal detection methods, including on-line access. The major concern of the Steering Committee, shared by many stakeholders, is the risk that the data released may be misinterpreted if its limitations are not recognised, see section 3.2.1.

One key objective for the Review was to consider whether widening access to the Yellow Card Scheme could improve protection of public health. The Scheme, initiated in 1964, was based on principles drawn up in the Dunlop letter circulated to all doctors and dentists (section 1.3.1; Annex C).

There is no support from stakeholders for any change to these principles. The Steering Committee are convinced that the underlying principles of the Scheme (section 1.2) should remain unchanged unless and until there is clear evidence that modifications to the Scheme would benefit public health. **Any amendments to the original principles must be subject to appropriate controls being in place which do not detract from the Scheme's ability to fulfil its original purpose.**

*'The most important point is to emphasise that the main objective of the Yellow Card System is to generate signals for rare adverse drug reactions (ADRs) which are unlikely to be detected by other methods of monitoring. Any change to the system must ensure that this objective is not compromised.'* Drug Safety Research Unit (Annex I).

There is wide support among stakeholders for optimising the use of the Yellow Card data for research and to protect public health, but the Steering Committee share stakeholders' concerns that any change to the Scheme must not deter reporters. It is essential that patients have confidence that their identity and personal data will not be disclosed for research based on Yellow Card data without their consent.

**A comprehensive communication strategy for health professionals and for the public will be required to provide a clear understanding of the reasons for any changes to the Scheme and purposes for which Yellow Card data may be made available.** The strategy should be designed to increase health professional and public awareness of the Scheme, to promote reporting and improve the quality of data captured.

*'In my view, for wider access to be ethical, reporters must be made fully aware of the uses to which the data might be put.'* Dr Patrick Waller (Annex I).

*'Nationwide publicity should be given to the intended use of data, as it is not practical to obtain individual consent from each patient.'* British Medical Association (Annex I).

### **3.1.1 Improving signal detection**

One reason for widening access to the Yellow Card database is to improve methods of signal detection.

*'An important element of research that is rather different to virtually all other applications of the database is research into the most efficient and effective ways of using the existing data to detect new 'signals' of potential new ADRs.'* Professor Stephen Evans (London School of Hygiene and Tropical Medicine) (Annex I).

Independent researchers could work with MHRA to identify new drug safety issues (undetected signals). This would improve public health and the future care of patients.

Independent research on the database could strengthen on-going monitoring of drug safety and be used by the pharmaceutical industry to examine the side effect profile of drugs in a specific class and thereby improve the safety profiles of new drugs under development. **A recognised process for accessing the data would avoid arguments over Freedom of Information (FOI).**

The Steering Committee is convinced that in the public interest Yellow Card data should be utilised for the maximum benefit to identify undiscovered ADRs. Although there are potential risks from widening access, section 3.5, the Steering Committee **recommends that there should be greater access to the Yellow Card data on condition that appropriate safeguards are put in place.**

*‘Provided that adequate scientific, ethical and data protection standards are applied, we do not think there is a risk to individuals from widening access to yellow card data. Indeed, we believe that appropriate research would improve the profile of the scheme and be to the benefit of public health and some would help the CSM and MHRA fulfil their statutory functions with respect to drug safety.’* British Pharmacological Society (Annex I).

### **3.2 SCIENTIFIC RESEARCH**

The prime purpose of the Yellow Card database is the detection of signals that suggest that there may be a drug safety issue. The benefits of research using large databases is clear from the findings from the three national longitudinal birth cohort studies of 1948, 1958 and 1970 (Douglas, 1948; Butler, 1958; Chamberlain and Chamberlain, 1970), and in medicines research from research on GPRD. From the latter there are over 200 publications in peer-reviewed journals<sup>18</sup>. Many stakeholders agreed that the Yellow Card database also has potential for use in research on ADRs and considered that it would be unethical not to allow greater access to the data.

*‘The refusal of the MHRA to release data for research purposes may be perceived as being obstructive and against the interests of drug safety and this would damage the scheme.’* British Pharmacological Society (Annex I).

*‘... it is also important to realise that if research that benefits patients is not carried out, then this itself is unethical.’* Professor Stephen Evans (London School of Hygiene and Tropical Medicine) (Annex I).

A few stakeholders were not in favour of greater access to the data.

---

18 GPRD website <http://www.gprd.com>

*'I consider that the wider release of these data goes against the spirit of the original scheme, and the data already provided will now be used for purposes that were not made clear when the doctors submitted the reports.'* Dr David Lott (Annex I).

*'The risks of misinterpretation and misunderstanding of independent analyses of the Yellow Card Data are very great and, in my view, of sufficient magnitude to advise against increasing access to this data resource.'* Scottish Medicines Consortium (Annex I).

There are limited ways of identifying patients who experience ADRs that result from genetic susceptibility or other rare personal idiosyncrasy. Research using Yellow Card data could identify such patients and thereby improve knowledge within specific therapeutic areas.

Potential uses of the database include analyses of case series, the comparison of ADR profiles of different drugs, identification of specific at-risk groups (sex- or age-related ADRs), complex drug interactions and their associated ADRs, ADRs related to different doses of specific drugs and ADRs caused through genetic susceptibility. The Steering Committee **recommends that the Yellow Card database should be further used for the purposes of research**, so that these research opportunities are available for independent researchers.

Widened access and use of the database for research will also encourage research co-operation and collaboration between MHRA and independent researchers.

### **3.2.1 Limitations on the utility of the database**

Stakeholders drew attention to several limitations on the use of the database for research. The Steering Committee recognises these will constrain use of Yellow Card data accordingly.

**Reporting by health professionals is entirely voluntary.** Although all those who prescribe medicines have, or should recognise that they have, a professional duty to report ADRs, reporting is not mandatory. Indeed, it is difficult to see how anyone could be compelled to report 'a suspicion'. Furthermore, experience in other countries of legally required reporting has not noticeably improved ADR reporting rates.

**Only a minority of ADRs are reported.** While estimated reporting rates vary substantially they may be as low as 10% (Belton et al, 1997) which illustrates the shortfall between ADRs and those Yellow Cards received by the MHRA and CSM. There is no information on the number of similar ADRs that are not reported, so numerator data is not complete and it is very difficult to determine denominator data against which the number of reported ADRs can be compared. Some Yellow Card reports omit relevant details about the ADR. It follows that the **database cannot be used in studies to determine the incidence of particular ADRs**, as reporting of some ADRs may reflect a high public profile rather than real incidence.

*'The data provided by the Yellow Card reports is essentially anecdotal and not amenable to epidemiological analysis. Its main function is signal (hypothesis) generation. If it is decided that access to Yellow Card reports should be widened then this major limitation must be made clear to those who wish to use the data set for research purposes.'* Dr Elizabeth Miller (Health Protection Agency) (Annex I).

If the Scheme is to be opened for wider use by independent researchers, **any researcher or investigator using the Yellow Card database must be aware of these limitations.**

*'It is important that the researcher is adequately qualified ... and can understand the strengths and limitations of the data the yellow card scheme provides.'* British Pharmacological Society (Annex I).

*'If public health is to be protected, it is vital that any Yellow Card data released is put into the context of exposure levels to the medicine, and consideration is given to the limitations of the data and that this is only one piece of evidence.'* GlaxoSmithKline (Annex I).

*'Any wider access, as much as the current access, must be accompanied by clear simple and unequivocal statements that reports are of possible and not of proven adverse effects.'* Professor Mike Langman (Joint Committee on Vaccination and Immunisation) (Annex I).

Unless these features are recognised, there is a real risk that erroneous conclusions could be drawn that would discredit the Scheme and do more harm than good. Any publicity given to such findings would cause unjustified anxiety for patients and prescribers, and result in some patients declining to take medicines that were, in reality, safe.

### **3.2.2 Patient consent**

There is a further limitation on research that requires the patient's consent. However, the well established ethical principles about consent apply to research on the Yellow Card database. Patients are not obliged to consent to disclosure of their personal information or to accept investigation purely for research purposes and must not be pressed to do so. These issues are discussed in section 3.8.

## **3.3 GENETIC RESEARCH**

One possible research use of the Yellow Card database concerns its potential in genetic research. The database could be used to identify ADRs occurring among patients with a genetic susceptibility. Adverse Drug Reactions can be divided into Type A (pharmacological, predictable, dose dependent) and Type B (idiosyncratic, unpredictable, not dose dependent) reactions. Type A reactions are more common and account for approximately 80% of all ADRs, as compared to 20% for Type B reactions. Certain factors such as pharmaceutical, pharmacokinetic and pharmacodynamic factors, in addition to drug-drug interactions, may predispose certain individuals to ADRs of Type A.



In addition, an individual's response to a drug and possible development of ADRs may be influenced by genetic make-up. Any individual may have specific genetic polymorphisms that predispose to a Type A reaction. Genetic deficiency of the cytochrome P450 enzymes, in particular CYP2D6, can lead to dose-dependent toxicity with some drugs.

The Yellow Card database could be used for genetic analyses, including searches for polymorphisms that influence drug response, and for genes that predispose an individual to disease. All genetic analyses require contact with the patient to obtain the necessary DNA from a blood, or other, sample which can be used to investigate the genetic basis of ADRs, or to identify specific genes that influence the efficacy of a medicine and to study interactions between medicines and disease genes. In order to use the Yellow Card database for such studies, a process of patient identification would be required to allow follow-up for DNA sampling and subsequent genetic screening. ADRs among patients exhibiting these features could be identified through the Yellow Card database, but would require the patient's consent.

As there are well established scientific and ethical principles in place for genetics research, the Steering Committee recommends **that any proposals for use of Yellow Card data should be subject to the same scientific and ethical scrutiny as all other genetic research proposals. The ethical principles set out by the Human Genetics Commission must apply to all forms of genetic research.**

While some stakeholders were not in favour of using the data for genetic research, 'Research that includes genetic information or analysis should not be permitted' Insulin Dependent Diabetes Trust (Annex I), the majority supported the proposal, subject to consent and ethical review.

*'Provided that care is taken to ensure that patients are not over-researched and the burden on any particular practitioner is limited, then research involving genetic information should be permitted.'* Professor Stephen Evans (London School of Hygiene and Tropical Medicine) (Annex I).

*'Research that includes genetic information would be traceable back to individuals and therefore should not be used without the consent of those individuals.'* Association for Nurse Prescribing (Annex I).

A specific consideration must be the implications that genetic research may have for relatives of patients. **The implications of any research for relatives should be considered by the scientific and ethics committees. When the scientific committee has before it a research proposal that includes genetic or other specialised research, the committee must ensure that it has amongst its membership sufficient experience to assess a research proposal involving any aspects of genetics, or co-opt a person with appropriate experience. The same principle applies to other specialised research.**

### 3.4 CONDITIONS AND LEVELS OF ACCESS TO YELLOW CARD DATA

Different legal provisions apply to identifiable and non-identifiable data. This is crucial to MHRA's legal obligation to withhold or disclose data requested for independent research on Yellow Cards, and for other purposes.

The Data Protection Act 1998 prohibits disclosure without consent of any personal information that identifies a person. The Act, therefore, applies to any information in Yellow Cards that has the potential to identify the patient whose ADR has been reported, unless consent has been given. The MHRA's legal advice is that provided a patient cannot be traced from the release of anonymised Yellow Cards, the obligation under the Data Protection Act to protect personal data is satisfied. The same principle applies to disclosure of details of the reporter.

The Freedom of Information Act will, however, require MHRA to make available aggregated anonymised Yellow Card data on request.

To satisfy both the Data Protection and the Freedom of Information Acts, Yellow Card data could be made available at different levels of detail. The Steering Committee has discussed this and recommends a three level categorisation as the basis for determining the conditions through which Yellow Card data might be released (Table 5, page 47).

The criteria which would determine whether data could lawfully be released are:

(i) could the information requested readily identify the patient or reporter, and (ii) would the research, for which disclosure is requested, involve consent from the reporter and/or the patient.

#### 3.4.1 Data Categories

**The first category would comprise aggregated anonymous non-identifiable data excluding all patient and reporter details.** There is no good reason for the MHRA to withhold such data. The level of aggregation is important and, provided the patient and the reporter cannot be identified, there is a strong FOI argument for proactive disclosure. As a matter of policy, the Steering Committee **recommends that MHRA should make available the maximum amount of data within this category through publication of data sets or in response to FOI requests.**

Quite a number of stakeholders supported this position. 'We do not believe that the sharing of aggregated anonymous data presents any ethical issues and we would encourage the CSM/MHRA to make this more widely available, eg via the internet.' British Pharmacological Society (Annex I). Another stakeholder was more cautious about the release of these data '... access to Yellow Card data by patients, either raw data or line listings, would not benefit patient safety since most patients do not have the knowledge and resources required to adequately interpret this data.' GlaxoSmithKline (Annex I).

On a pragmatic level, publishing all aggregated and unidentifiable Yellow Card data for all drugs licensed in the UK would be an enormous task. Therefore, only data on specific drugs of general interest should be regularly published, including black triangle (▼) drugs and drugs for which the MHRA and CSM have received the greatest number of ADR reports per month. The Steering Committee **recommends that, wherever possible, anonymised aggregated data should be regularly published on the MHRA website accompanied by guidance on interpretation. The frequency of updating would depend on the rate at which the data profile changes, but in considering the range of data placed on the website and the frequency of updating, the MHRA should bear in mind that feedback undoubtedly improves reporting rates (section 3.13). Other data sets that are not regularly published should be available on request, under FOI.**

Requests for unpublished aggregated anonymised data sets, and those for older drugs, would be available on request at the fee scale set for FOI provision of information. The fee scale should be published by MHRA.

**The second category would include the information contained in individual Yellow Cards, but patient and reporter identifiable data would not be included.** This category would include details of case reports with patient age range and sex, dates of drug administration and reaction, concomitant medication details and the patient's past medical history, but no details that could lead to identification of the patient.

The third level, **Category III, would enable the person receiving the data to request from the reporter further information about the patient.** In other respects Category III would be similar to Category II, but the difference between them is the intention of the researcher in this category to make contact with the reporter via the MHRA to obtain more details of the patient.

The Steering Committee **recommends that research proposals that involve access to individual Yellow Card reports in Categories II and III should be subject to independent scientific and ethical scrutiny by appropriate bodies,** see sections 3.5 and 3.6. This proposal has wide support among stakeholders.

*'... it is important and in the public interest that the data should be made available for bona fide researchers conducting good quality scientific research that has been properly peer reviewed and received appropriate ethical approval.'* British Pharmacological Society (Annex I).

The Steering Committee also recommends that **scientific appraisal of a research proposal should precede ethical review.**

The anonymity of both reporter and patient remain paramount in Category III. The disclosure of details is not acceptable unless the reporter has agreed that it would be appropriate for the patient to be asked for consent.

This issue was considered to be of significant importance by a number of stakeholders.

‘Breaking the confidentiality of the personal details of the reporter can have disastrous consequences for both the reporter and the Scheme. . . . Such access should always require complete control or even go-between of MHRA staff between reporter and investigator. Any other direct access to the reporter will undoubtedly have negative consequences to the scheme.’ Johnson & Johnson (Annex I).

‘The patient should be approached by the reporter who should in turn be approached initially by the MHRA and not directly by the researchers.’ British Pharmacological Society.

‘An issue to consider is how the researcher gets access to the patient sample. The initial contact between the researcher and reporter will have to be via the MHRA. Patient contact will have to be made via the original reporter or via the patient’s GP. In this situation, it may be possible to make use of the RMCs – indeed, in the whole process of contacting the reporter and recruiting the patients, the RMCs could play a crucial role and this should be considered further in the review process.’ Professor Munir Pirmohamed (SCOP member, RMC head) (Annex I).

The Steering Committee recommends that the **MHRA should act as an intermediary between the researcher and the reporter for proposals in Category III**. It should be the MHRA’s responsibility to ask the reporter if they consent to their details being passed to the researcher. If the reporter agrees, the researcher can then make direct contact with the reporter and through the reporter contact the patient for consent for further information and/or investigation.

There will inevitably be extra work for a reporter who is willing to contact a patient about their possible involvement in Yellow Card research. The Steering Committee proposes that in these circumstances the reporter should receive a fee. This proposal is described in full at section 3.11.5.

Table 5 summarises how requests for access in the three categories might be managed.

<b>Table 5 Categories of Yellow Card Data</b>		
	<i>Type of Data Released</i>	<i>Scientific and Ethical Review</i>
Category I	Aggregated anonymous data	No
Category II	Case reports without reporter and patient identifiable details	No*
	Case reports without reporter and patient identifiable details	Yes
Category III	Case reports involving the proposed release of reporter and patient details	Yes

\* Subject to fulfilling a set of criteria established by the scientific committee

### 3.5 SCIENTIFIC APPRAISAL

Many stakeholders expressed concern that if data from individual Yellow Cards were to be released, this should only be after scientific scrutiny of the purposes for which the data were requested and of the research methodology.

*‘The establishment of a (sic) independent committee to review the scientific merit of projects and to advise on how these might be prioritised by the MHRA should be considered. ... The Society would support the establishment of an independent scientific committee to oversee this process.’* British Pharmacological Society (Annex I).

Three main reasons lie behind the emphasis that stakeholders give to robust scientific scrutiny. First, the Yellow Cards and the information they contain were provided on a confidential basis. Secondly, any data disclosed must not lead to identification of individual patients or reporters without consent. Thirdly, there is a risk of misinterpretation of data released because the limitations on its use are not recognised. With regard to the last factor, some stakeholders suggested that without proper scientific scrutiny of research proposals, unjustified health scares could follow the release of data to those who failed to appreciate the limitations on its use (section 3.2.1).

Stakeholders were also concerned that Yellow Card data might be used inappropriately, for example for direct financial gain, for commercial advantage, in medico-legal actions or by pressure groups.

*‘Data from the Yellow Card Scheme should not be made available for financial gain, either direct or indirect gain.’* Insulin Dependent Diabetes Trust (Annex I).

*‘Researchers should not be allowed to profit financially from use of the data, as this would deter future reporters (who gain nothing financially from reporting).’* Guild of Healthcare Pharmacists (Annex I).

Others considered that ‘it would be impossible to prevent financial gain if access to the data is broadened. For instance genotyping could lead to a diagnostic being developed with a medicine providing safer use of that medicine and thus potential financial gain for the company. We believe that potential financial gain should not preclude availability of the data. ... The issue of financial gain would also be taken into account by the independent ethics committee when considering the research protocol.’ Association of the British Pharmaceutical Industry (Annex I).

The Steering Committee recommends that the Yellow Card data should not be used for direct financial gain (section 3.10.4).

As these are legitimate concerns the Committee **recommends that scientific safeguards must be put in place to protect patient confidentiality and to ensure that data are only**

**released for research and other purposes that have been independently evaluated.** The Committee recognises it would be perverse if an unfounded health scare were to result from misinterpretation of Yellow Card data.

The Steering Committee's proposals for scientific safeguards to be exercised through an independent scientific committee, and the committee's functions, are set out in section 3.10.

The Steering Committee recommends **that requests for data not subject to FOI and for data from individual Yellow Cards should be assessed by an independent scientific committee set up by the Licensing Authority to ensure that proposals for research using Yellow Card data are scientifically robust.**

### 3.6 ETHICS

**Ethical considerations apply to all identifiable data** but not to aggregated anonymised Yellow Card data as defined in Category I (section 3.4.1). Since individual patients or reporters cannot be identified, such data can be released without consent in accordance with FOI.

Other issues that would require appraisal by an ethics committee, including patients' consent, use of the data for audit purposes and charging for use of the data, will be explored further in sections 3.9 and 3.11.5.

Requests for data in Category III will always require ethical review as the researcher's purpose will be to obtain further information about a patient from the reporter and in some cases will involve the researcher contacting the patient. All proposals in Category III must be subject to ethical review by an appropriate ethics committee.

In Category II, referral for ethical review may be needed when release of anonymised individual Yellow Cards is requested and the data include particular patient characteristics. Other data requests in Category II will not require referral for ethical review. However, in cases of uncertainty the presumption should always be for referral to an ethics committee.

The ethics committee would be responsible, as in other spheres of medical research, for considering each research proposal on a case-by-case basis to determine whether access to the requested data is ethical for the intended purposes.

Stakeholders offered different opinions about how ethical review should be organised for research on Yellow Cards.

*'The ethical issues of widening access of the data need to be considered, there will need to be an*

“ethics committee”, possibly linking in with the MREC committees that run within the NHS. It is essential that individuals with experience and expertise in assessing research proposals in the NHS are involved in the ethics issues linked to wider access of the Yellow Card data.’ North West Medicines Information Centre (Annex I).

‘We do not believe that the current MREC electronic application form would lend itself to review of yellow card data proposals nor do we believe that current MREC membership is skilled in issues of pharmacovigilance. Therefore we would favour the development of a specialist independent body to review all yellow card database proposals. We believe that the body appointed should be independent of the MHRA to avoid any potential conflicts of interest.’ Association of the British Pharmaceutical Industry (Annex I).

One option would be to separate entirely scientific and ethical review. This could be achieved through use of Main Research Ethics Committees (Main RECs), previously known as Multi-centre Research Ethics Committees (MRECs), under the established framework of the Central Office for Research Ethics Committees (COREC) system. Ethical review of research proposals to use Yellow Card data would fall under the umbrella of Main RECs rather than Local RECs, as the Yellow Card Scheme collects data from all over the UK.

The second option would involve MHRA and CSM setting up a scientific/ethics committee, similar in function and role to the Scientific and Ethical Advisory Group (SEAG) used to assess research protocols for the General Practice Research Database (GPRD).

The Steering Committee recommends the first option for three reasons. First, the appraisal of science and ethics are separate functions and are maintained as distinct in other spheres of medical research.

Secondly, within the current NHS research governance and legal framework, any independent ethics committee must be accredited by the UK Ethics Committee Authority. As almost all the Yellow Card reports relate to treatment provided in the NHS, the ethics committee to review research using Yellow Card data must be compliant with the most recent version of the Research Governance Framework for Health and Social Care<sup>19</sup>. Advice from COREC suggested that Ministers expect all research affecting NHS patients to be considered by an ethics committee within the COREC system.

Thirdly, the use of the Main RECs would demonstrate that the ethical review procedure is transparently independent from the MHRA and CSM.

---

19 Draft second edition, April 2003 <http://www.doh.gov.uk/research/documents/rd3/rgf2ndeditionv22300403.doc>

The Main RECs and Local RECs provide guidance on the ethics rather than the science of research proposals. Under the COREC system, the Steering Committee was informed that the RECs are no longer permitted to ask for changes to the methodology once a proposal has been scientifically assessed and accepted.

A further benefit of using the COREC system is that it would enable any scientifically approved proposal to be allocated and considered by a Main REC within a specified time frame of 60 days. This feature reinforced the Steering Committee's conclusion that the scientific scrutiny of Yellow Card research proposals (section 3.5) should always precede referral for ethics committee approval.

The Steering Committee recommends that where **appraisal of ethical issues is required (all Category III and selected Category II requests), this should be carried out separately and independently of scientific appraisal and that the appraisal should be undertaken through the COREC system. A Main REC must be consulted about any proposed research that may involve access to a patient or procedures that require consent, including personal information about the patient known to the reporter, or other procedures that under normal conditions require ethical approval.** Over time, one Main REC may take a particular interest in Yellow Card research.

The Steering Committee emphasises that **independence of both committees from the MHRA and CSM is of great importance in order to avoid allegations of bias.**

### 3.7 CONTROLS ON RESEARCH USE OF YELLOW CARD DATA

There are different ways in which access to Yellow Card data could be controlled. One restrictive option would be to provide data to independent researchers provided they undertook the research jointly with, or supervised by, MHRA.

A second, slightly less restrictive, option would be to require independent researchers to have training from MHRA so that the limitations of the Yellow Card database are fully understood before any data are released to them.

These options could help ensure the appropriate interpretation of the data but would have resource implications for the MHRA. The **major objection to both is the lack of independence from MHRA.** The Steering Committee's conclusion is that **both options must be ruled out** as the objective of the Review is to consider how best independent research on the Yellow Card database can be organised.

The GPRD follows a different model as a database supported by systems that ensure control on data access. In the GPRD system there are a number of levels of access and the level determines the quantity of information provided. Research protocols requesting



access to the GPRD database are scrutinised by the unified Scientific and Ethical Advisory Group (SEAG). The Steering Committee does not consider this model of control to be appropriate for Yellow Card data for the reasons given in section 3.6.

Stakeholders generally expressed a preference for an independent scientific appraisal system.

*'Since the data will presumably continue to be held by the MHRA/CSM, to which applications would be sent, it would be important that the system for granting access should have a measure of independent scrutiny.'* Department of Health (Annex I).

*'We believe there should be consideration given to setting up an independent committee that would be responsible for setting out broad guidance on who should be allowed access to information and under what circumstances. Factors such as the balance between 'lay' and 'expert' members, whether the committee sets general guidelines or considers individual research proposals and how it is funded, as well as transparency and accountability will be critical in establishing its independence and perceived trustworthiness.'* Consumers' Association (Annex I).

The Steering Committee recommends that **an independent scientific committee should be appointed by the Licensing Authority with responsibility to ensure that proposals for research using Yellow Card data are scientifically robust.**

The scientific committee will also need to consider whether the research is of sufficient value in public health terms to justify the release of potentially identifiable information, and whether the principal research applicant understands the constraints on the use of the data and has the experience necessary to interpret the data appropriately. These considerations must precede referral to an ethics committee.

### **3.7.1 Who can request Yellow Card data**

Some stakeholders argued that access to Yellow Card data should in principle be restricted to individual researchers and organisations with an established track record in research on medicine safety.

*'Information could be used to enhance patient safety and public health if it was more readily available to other approved sources. These sources should include health professions and not private companies. ... No problems are envisaged in offering wider access to yellow card data if this falls within the NHS or allied health professions.'* Association for Nurse Prescribing (Annex I).

Other stakeholders did not want any restrictions on who might request Yellow Card data, provided suitable safeguards are in place.

'It would be better to come clean and allow all-comers to use the data, but to assess all applications through the ethics/review group ... in order to ensure appropriateness of use.' Dr Keith Beard (SCOP member) (Annex I).

Under FOI there are no restrictions on who may request data. The Steering Committee concluded that in principle there should be no restrictions on who may apply to undertake research, as opposed to separate systems for researchers, companies and investigative reporters. All proposals should be considered under the same conditions and each proposal reviewed *de novo* on its own merits, regardless of the status or previous experience of the applicant.

To provide the necessary scientific and ethical safeguards, the Steering Committee recommends that **access to the database should be managed through a single central system. There should be no by-pass mechanisms or exemptions. The scientific committee should consider all proposals under the same set of rules, irrespective of their origin.** Any individual or organisation should be free to apply and their proposal should be approved or refused through the independent scientific committee and Main REC. **Any research collaboration between the MHRA and researchers would also be subject to the same criteria.**

Stakeholders have emphasised the importance of maintaining anonymity for the patient and the reporter. When the scientific and ethics committees authorise research that involves Category III data, there must be systems in place to ensure that the researcher has made proper data security arrangements to avoid the risks of patient identification.

### 3.7.2 Publication of independent research

The consequences of independent research on Yellow Card data could result in findings that call in question the safety of a licensed medicine. In this situation the researcher will normally wish to publish the findings promptly; if the investigation was sponsored, the research sponsor will wish to publish or disseminate the findings without delay. However, immediate publication without any opportunity for the results to be properly and independently assessed poses two problems.

First, it is essential that any research that calls in question the safety of a licensed medicine must be considered before publication by CSM and MHRA. In some cases urgent regulatory action may be needed. Should a product licence be withdrawn, public health authorities may need to arrange for alternative products to be available for patients who require continued medication.

Secondly, there have been some well publicised occasions where misleading findings and/or ineffective communication of the results of research have caused public alarm and

avoidable harm to patients who stopped taking medicines, when the research findings did not justify this.

Several stakeholders expressed concern about both these possibilities and suggested a contract be drawn up between researchers and the scientific committee and MHRA concerning the release of findings using the Yellow Card data.

*‘Persons permitted to access the data should need to sign that they understand its nature and its limitations and that they agree to stay within the boundaries this imposes on its interpretation and communication in presentations and publications.’* Novartis (Annex I).

*‘One option is that, before individuals access the data, they could sign a declaration that they will use the data in accordance with a written code of conduct. The code of conduct could emphasise that the use of the data is for the benefit of individual patients or groups of patients. It could also emphasise that the data will not be used commercially to promote one product over another product or be included in commercial literature.’* National Patient Safety Agency (Annex I).

*‘To protect the integrity of the system we would envisage that users would need to be registered and would need to declare the purpose for which they requested the access and sign an agreement that their use would be solely for the declared specific purpose and strictly no other uses would be permitted.’* Novartis (Annex I).

The Steering Committee is conscious that any form of pre-publication scrutiny of research reports may be regarded as ‘censorship’ and it may be claimed that research on the Yellow Card database has ‘strings attached’. Nevertheless, as a safeguard, the Steering Committee recommends that **all researchers should be contractually required, within a defined period of time prior to publication, to notify the scientific committee, Main REC and MHRA of their intention and plans to put their findings in the public domain, and provide copies of their draft publication**<sup>20</sup>. The Steering Committee recommends the defined period should be 28 days.

The Steering Committee also recommends that **if research findings call in question the safety of a licensed medicine, the findings should be considered without delay by the CSM and MHRA**. The embargo on publication within the defined period must continue until CSM and MHRA have considered the need for regulatory and/or public health action. The MHRA will have responsibility for informing the marketing authorisation holders (MAHs) who hold the product licence of the drug implicated in the proposed publication.

When the scientific committee considers that the research findings require further investigation and/or peer review, the committee should encourage the researcher to submit

---

20 Publication includes all forms of media (documents, television scripts, via the internet etc.)

his findings to these independent procedures. If this proposal is not taken up (and to avoid public alarm that may not be justified), the committee should inform CSM and MHRA.

*'If data is released to researchers then vetting of the use of this data e.g. publications could be done by the MHRA.'* North West Medicines Information Centre (Annex I).

*'Another option would see the MHRA requesting to be sent in advance those draft papers for publication that include reference to yellow card data.'* National Patient Safety Agency (Annex I).

*'We believe that this is a desirable option and it should be possible as generally publication timelines are known well in advance by the author. The one exception would be publication in the national media which would be more difficult to delay but providing a report in advance to the MHRA and the relevant company could be made a condition of approval of the research proposal. It is common for companies to have a clause in contracts between companies and institutions where investigator-led research is being supported by the company to allow the company a period of time (often 30 – 60 days) to comment on proposed publications arising from the research. The ABPI and Department of Health launched a Model Clinical Trial Agreement in January 2003. The MCTA has a section in it on publication practice and allows the sponsor up to 60 days to review any proposed publication by the investigator.'* Association of the British Pharmaceutical Industry (Annex I).

While there can be no justification for censorship or suppression of research that has been carried out to high scientific standards, the Steering Committee considers these procedures are necessary, (i) to ensure the validity of research based on Yellow Card data, (ii) to allow time for any regulatory or public health action and (iii) to reduce the risks of unjustified public alarm resulting from publication of unvalidated results.

The scientific committee, CSM and MHRA should, if they wish, provide comments and feedback to the researcher on his findings and proposed publication. The researcher should not, however, be contractually obliged to accept these as a precondition for publication after expiry of the defined period.

Whenever independent research identifies a previously unrecognised and significant ADR, it will be important for the embargo on publication to be lifted as soon as the procedures described above can be completed before expiry of the 28 day period.

### **3.8 CONSENT**

The principles of consent for research based on Yellow Card data are the same as those in other spheres of medical research. The patient has a fundamental right to maintain control over research that uses his personal data, and over any procedure carried out on his body, including blood sampling. There is one practical difference for research using Yellow Card

data. The reporter is the only route through which a researcher can make contact with the patient to obtain his consent.

### 3.8.1 Initial submission of a Yellow Card

The Yellow Card Scheme does not require the reporter to obtain the patient's consent before submitting a Yellow Card about an ADR. Since September 2000, Yellow Cards have been submitted anonymously, the reporter providing only an identifier but no personal details (section 1.4.6). The procedure satisfies the Data Protection Act 1998 and means that informed consent is not legally required before a Yellow Card is submitted.

*'Health professionals should therefore have the right to report suspected adverse reactions without the consent of the patient.'* Medicines Commission (Annex I).

While the patient may not have the legal right to be told when a Yellow Card is submitted, the Steering Committee considers that **it would be good practice for the reporter to inform the patient that he is submitting, or has submitted, a Yellow Card**. There will, however, be occasions when the reporter decides this is not in the patient's best interests.

The available information indicates that, in the majority of cases, Yellow Cards are submitted without the patient's knowledge. Many reasons are given by healthcare professionals for not reporting ADRs at the time of consultation with the patient. For example, it may not be practical to complete the card with the patient present because of the time it takes to complete a Yellow Card, or the reporter may not consider the patient's condition to be an ADR at the time of consultation. Other reasons for not reporting ADRs are outlined in the National Audit Office (NAO) report<sup>21</sup>.

Stakeholders' responses also indicate that, if patient consent were made mandatory before a Yellow Card was submitted, a reduction in the number of Yellow Card submissions would inevitably follow. This would jeopardise the future of the Scheme.

*'It is possible that introducing a process of obtaining consent prior to submitting a Yellow Card will have a negative impact in terms of reducing the numbers of cards provided to the MHRA/CSM. However, it may also have the opposite effect, resulting in increased awareness – and reporting – of adverse effects from medicines.'* Consumers' Association (Annex I).

The Steering Committee acknowledges that there are practical difficulties in informing a patient who is not available at the time the reporter decides that a Yellow Card should be submitted. However, there is no reason why the reporter should not inform the patient at the next convenient opportunity and this would also be good practice.

---

21 'Safety, Quality and Efficacy: Regulating Medicines in the UK' NAO Report published 16 January 2003

Conversely, there could be circumstances when a patient might not want an ADR to be reported to the Scheme, while the reporter believed a Yellow Card was required for the greater public benefit. There are very few circumstances in which a patient's instructions can be disregarded, but the law and professional guidance do allow exceptions when this is in the public interest.

Taking all these considerations into account, to protect the Scheme and to avoid changing the Scheme in a way that might discourage some reporters, the Steering Committee recommends that current practice should continue. **Health professionals should not be required to obtain the patient's consent before submitting an anonymous Yellow Card.**

There may be other situations when a patient wants a health professional to submit a Yellow Card but the health professional considers there has been no ADR to report. In these unusual circumstances, a health professional should be under no obligation to comply or submit a Yellow Card against his professional judgement. Equally, the patient must be free to approach another recognised reporter to the Scheme.

Alternatively, if the Steering Committee's recommendations about patient reports, section 3.12, are adopted, the patient will be able to submit a patient report directly to the CSM and MHRA.

### **3.8.2 Research use of individual Yellow Cards**

For the reasons set out above, consent is not required for the initial submission of a Yellow Card. However, any opening of the Yellow Card database in the way the Steering Committee proposes, will result in researchers requesting personal and other data about some patients whose ADRs have been reported in the Scheme. The Data Protection Act 1998 prohibits disclosure of such data without the patient's consent.

**The patient must, therefore, provide fully informed consent for any use in research of their personal or identifiable information and, for obvious reasons, for their physical participation in research.**

Valid consent can only be given prospectively and after the reasons for asking the patient for consent have been explained so that the patient's decision is 'informed'<sup>22</sup>. The patient's

---

22 Article 22 of the Declaration of Helsinki by the WMA clearly requires that consent is given before individuals participate in research: 'In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.'

retrospective acceptance of disclosure of personal data by the reporter for research purposes does not constitute consent<sup>23</sup>.

When consent is requested, **the reporter will normally be in the best position to explain the research to the patient and then to ask for consent. If a patient refuses to give consent, that decision must have no influence on the patient's current or future clinical care.** On some occasions the reporter may decide the patient should not be asked because of their medical condition or personal circumstances.

Before the patient can be approached, the researcher will need to know the identity of the reporter. The Steering Committee recommends that **when the scientific committee and Main REC authorise research that requires contact between the researcher and the reporter, the MHRA should act as an intermediary between them and the MHRA must make the initial contact with the reporter.**

In almost all cases it would be considered good practice to contact the patient's GP as, in most cases, the GP will hold further details of the patient. **When the reporter is neither the prescriber nor the patient's general practitioner, the Steering Committee recommends that the reporter should pass the request for access to the patient's general practitioner.**

For all types of genetic research, because of possible wider implications for the patient's relatives, it will be particularly important that the reasons for the research are fully explained before consent is requested. The patient's physical participation will, of course, be necessary if DNA sampling forms part of the investigation. **For genetic research, the Main REC will have taken into consideration the possible implications for other family members.**

Established medical research protocols and ethical guidance are available and apply to research involving children, when it would be appropriate to obtain the agreement of a parent or guardian. The same principle applies to research that involves the disclosure of information about adults who are themselves unable to give valid consent.

The possible addition of a tick box on the Yellow Card for the reporter to record that a patient is, in principle, willing to be contacted for more information could facilitate research into unusual or rare ADRs.

*'In the future simpler ways of obtaining consent prospectively may emerge which could include an option to include or opt out of say genetic information. These could perhaps involve future modifications of the Yellow Card to record the consent of patient and reporter at the time of reporting.'* Novartis (Annex I).

---

23 'It is a commonplace in the modern discussion of research ethics that retrospective consent is not consent, but at the most acquiescence' in Cave E, Holm S, Milgram and Tuskegee. *Paradigm Research Projects in Bioethics. Health Care Analysis* March 2003; 11 (Issue 1), 27–40.

A tick box may be helpful in the future, but on its own would not constitute adequate consent. The reporter or the general practitioner will still need to confirm the patient's consent when the particular reasons for the research are known.

### 3.9 AUDIT

A fundamental principle in Sir Derrick Dunlop's original letters of 1964 (Annex C) is that the Scheme would not be used for enquiries about prescribing costs or for disciplinary purposes; *'The Health Ministers have given an undertaking that the information supplied will never be used for disciplinary purposes or for enquiries about prescribing costs'*. The use of Yellow Card data for audit must be considered in the context of Sir Derrick's undertakings.

Stakeholders did not support any changes to the original principles and the Steering Committee has recommended that these should remain unchanged. Reporters who have submitted Yellow Cards to CSM and MHRA since 1964 did so believing that these undertakings would be honoured. The retrospective use of Yellow Cards for purposes that broke Sir Derrick's undertakings would, at best, undermine or could destroy the credibility of the Scheme. **The Steering Committee is convinced that Sir Derrick Dunlop's original promise must be honoured.**

The reason for considering the use of Yellow Card data for audit follows requests from NHS authorities to use the data for their own audit purposes. Primary Care Trusts (PCTs), Operating Divisions (Scottish Primary Care Trusts) and other NHS Trusts have requested that data for their respective areas should be routinely available to them.

In 1964 audit was not an issue for the NHS, whereas in 2004 it is a central responsibility both for NHS managers and clinicians. Clinical audit is now an integral part of clinical governance, and some NHS Authorities suggest that data from the Yellow Card Scheme could contribute to their governance procedures.

Stakeholders' views are divided on the use of Yellow Card data for audit. Some consider the Dunlop principles preclude all types of audit. Other stakeholders would allow data to be released for some, but not all, types of audit. For example, release of data for audit designed to support professional education and training would be accepted, whereas data for management audit or for audit of prescribing patterns and costs would not.

*'We consider that one of the most contentious issues is that Yellow Card data might be used for "management" purposes. This is a major departure from the original reassurances given by Sir Derek (sic) Dunlop. ... There does not appear to be sufficient potential benefit from such proposals to outweigh the advantages of a wholly voluntary scheme, free from any kind of pressure. A major analogy is the aviation world model of "near miss" reporting, which depends wholly upon very*



similar dynamics. The College therefore opposes the use of data for such “management” purposes.’ Royal College of General Practitioners (Annex I).

*‘It would be unwise to have drug/reaction combinations given by small geographic area both because this may lead to identification of individual doctors or of individual patients, but also the utility of finding differences is very limited. In order to preserve confidentiality of the system it is important that doctors do not feel that they are being watched through the Yellow Card system otherwise this made calls (sic) a breakdown of confidence held by doctors in the CSM. At the same time it does seem reasonable to encourage NHS trusts and primary care trusts to pass on the message that the reporting of suspected adverse drug reactions is a public health benefit and while it is not compulsory in (sic) should be seen as something that is easy to do and brings benefit to all concerned.’* Professor Stephen Evans (London School of Hygiene and Tropical Medicine) (Annex I).

Stakeholders who are against the use of Yellow Card data for any type of audit argue that this purpose is incompatible with the undertakings given by Sir Derrick Dunlop. They also question how meaningful such data could be to NHS Trusts who wish to use Yellow Card data as a performance indicator, as it is unknown whether specific areas are experiencing fewer ADRs through better clinical practice or are not reporting for various reasons.

Another major stakeholder concern is that release of data for audit will deter reporters from submitting Yellow Card data and thereby harm the Scheme.

*‘There is a risk that trusts with low levels of reporting might badger their staff to complete reports. Given the voluntary nature of the scheme, this could have an opposite effect to the one desired.’* Dr Patrick Waller (Annex I).

Stakeholders who support data release for professional education purposes suggest that, subject to proper safeguards, audit could encourage ADR reporting. Audit could provide NHS Authorities and Trusts with an indication of which of their centres have low ADR reporting rates. Professional education and training could then be better targeted to encourage reporting by these centres.

There is no stakeholder support for the release of Yellow Card data for managerial audit, and particularly not for audit of clinical practice. The latter is uniformly considered to compromise the principle that the data would never be used for disciplinary purpose or enquiries about prescribing costs (Annex C). There is also concern that the use of Yellow Card data for audit in areas with small populations could compromise patient anonymity by linking Yellow Card data to local databases.

The Steering Committee deliberated on the range of stakeholder views and whether the release of any Yellow Card data for audit purposes was practicable without compromising the Dunlop undertakings or jeopardising the future of the Scheme.

In considering if Yellow Card data should be available for audit, one factor is clear. Under the Freedom of Information Act, NHS Trusts will shortly be able to obtain aggregated anonymous Category I data (section 3.4.1). It is unlikely that Category I data alone will satisfy NHS authorities and other stakeholders who consider audit for professional educational purposes.

The central questions are, therefore, should access to data in Categories II and III (section 3.4.1) be permitted for audit purposes, and if so, should the data be available for all types of audit.

The Steering Committee has already recommended that *'any individual or organisation should be free to apply and their proposal should be approved or refused through the independent scientific committee and Main REC'*, section 3.7.1. If that recommendation is accepted, NHS authorities' requests for data in Categories II and III should not be arbitrarily excluded. Requests from NHS authorities for data for audit purposes should be considered on their merits by the independent scientific committee and Main REC.

*'NHS Trusts/Primary Care Trusts requesting access to data should only be granted access where their enquiry is linked to an approved research programme.'* Association for Nurse Prescribing (Annex I).

NHS audit proposals for managerial purposes are not normally subject to review by ethics committees unless these involve the audit of patient treatment and care and/or the use of patient identifiable information subject to data protection. The boundary between managerial audit and audit of clinical care can be blurred, and as some NHS audit proposals merge different types of audit, all proposals to use Yellow Card data for audit should be reviewed by a scientific committee and Main REC.

In considering NHS data requests for audit purposes, the scientific and ethics committees will need to consider the purposes for which the data will be used and if these comply with the Dunlop principles. This will be particularly relevant to requests for Category III data as it will be essential to maintain patient anonymity to avoid the possibility of Yellow Card data being used in the audit of clinical care for NHS disciplinary purposes.

The Steering Committee considers that **provided the scientific and ethics committees are satisfied that (i) a specific proposal complies with the Dunlop principles, and that (ii) the application is scientifically and ethically acceptable, there is no reason that would justify the arbitrary exclusion of proposals to use Yellow Card data for audit purposes.**

In this recommendation, the Steering Committee recognises there could be benefits for public health and to the Scheme itself from audits designed to improve professional education and to improve ADR reporting rates.

### **3.10 THE INDEPENDENT SCIENTIFIC COMMITTEE; MEMBERSHIP FUNCTIONS, RESPONSIBILITIES AND CONDITIONS FOR RESEARCH ACCESS**

Earlier sections of this chapter have considered the categorisation of Yellow Card data, section 3.4.1, the need for an independent scientific committee, section 3.5, ethical review, section 3.6, and the arrangements to obtain consent from the patient, section 3.8. This section describes in more detail features of the scientific committee and its functions that were not included in earlier sections.

#### **3.10.1 Appointment and composition of the independent scientific committee**

The Steering Committee recommends that the **Licensing Authority should appoint the committee**. The independence of the scientific committee from the CSM/MHRA will be crucial to the credibility of the system. The scientific committee should be responsible for, and advise Ministers on, the suitability of individual research proposals for access to the Yellow Card database.

The membership of the committee should be multi-disciplinary and include experts in disciplines related to drug safety and ADRs who must be conversant with the potential and limitations of the data held in the Yellow Card Scheme.

The committee should include lay members to ensure that patients' interests are properly represented.

If there is no relevant expertise among its membership, the committee should co-opt a person with the relevant experience when a specialised proposal is to be considered. This will be important whenever genetic proposals are assessed.

#### **3.10.2 Scientific appraisal**

Stakeholders offered many suggestions on the mechanisms needed to evaluate research proposals that plan to use Yellow Card data, section 3.7. Based on stakeholders' comments the Steering Committee recommends that:

- **the scientific committee must have sole responsibility for evaluating the scientific merit of research proposals that would require the use of Categories II and III Yellow Card data.** The MHRA should have an opportunity to offer comments but the scientific committee must be free to accept or discount these;
- **to manage straightforward research proposals that request Category II but not Category III data, the scientific committee should develop a set of criteria.** Requests for Yellow Card data for proposals that satisfy these criteria could be

released by the MHRA without the need for all Category II proposals to be considered by the scientific committee. The committee should be informed of all such data released by the MHRA;

- **the scientific committee should publish the criteria and its other rules of procedure for data release. These criteria must not permit the release of reporter or patient identifiers** and should ensure that criteria for release of Yellow Card data are applied uniformly and irrespective of the applicant's status;
- **the research applicant should be accountable to the scientific committee and be provided with clear terms and conditions setting out the purposes for which the Yellow Card has been released.** These should include firm guidance on release of data to third parties and data storage conditions;
- **genetic research proposals should always be considered by the scientific committee and Main REC**, see section 3.3;
- **for research applicants whose requests for Yellow Card data are refused, an appeal mechanism should be available** but limited to those who can show that they have good cause to challenge the scientific committee's decision. The appeal procedure could be similar to that already in place for the MHRA's statutory committees;  
*'Any decision to withhold data should be subject to appeal to an independent body.'*  
Dr Andrew Herxheimer and Mr Charles Medawar (Annex I);
- **the scientific committee should prepare an annual report for the Licensing Authority.** The report should set out the annual number of research proposals accepted, rejected and appealed, and should be published on the MHRA website.

### 3.10.3 Research involving vulnerable groups or with a fatal outcome

For some patient groups, and for Yellow Cards reporting a fatal outcome, the normal arrangements for consent cannot be followed. The scientific committee and Main REC will have to consider the issues posed by such research requests on a case-by-case basis. There are well-established professional guidelines to assist reporters and researchers in these circumstances.

### 3.10.4 Financial gain from research on Yellow Cards

Stakeholders drew attention to the voluntary arrangements for reporting ADRs to the Yellow Card Scheme. As the Scheme depends on the good will of reporters, there is particular concern among stakeholders that data from the Scheme should not be released for research that would have a direct financial benefit to the researcher or the research

sponsor. There was also concern about indirect financial gain but stakeholders recognise that this possibility cannot be entirely avoided.

The Steering Committee recommends that **the scientific committee and Main REC should not authorise the release of Yellow Card data for direct financial gain to researchers or research sponsors.**

To reduce the potential for significant indirect financial gain by researchers or research sponsors, the scientific committee and Main REC should also consider the need to apply conditions to research proposals that appear designed or are likely to result in substantial indirect financial gain. The Steering Committee acknowledges that this is a difficult area but endorses stakeholders' concerns that the data are provided to the MHRA voluntarily, free of charge and for public benefit, and should not be released for individual or corporate financial gain.

### **3.10.5 Requests for access to the whole database and for on-line access**

The MHRA has received requests for access to the entire Yellow Card data set and/or on-line access. Some of these requests come from researchers who propose to develop new methodologies for signal detection. These proposals would involve the release of reporter identifiers and, as such, should be considered as a special type of Category III application and reviewed in the same way.

If an independent researcher is given access to the whole Yellow Card data set there will inevitably be a potential risk of disclosure to a third party. Other potential risks are that a researcher might make an unauthorised approach to a reporter or to a patient whose personal particulars had mistakenly been included in a Yellow Card.

On-line access carries greater risks. The MHRA would no longer have total control of the database. The data might be used for purposes that had not been referred to, or approved by, the scientific committee and Main REC. Unauthorised use or release of part of the database to a third party would destroy the credibility of the Scheme. These risks, however unlikely, must be recognised. Their realisation would have devastating and permanent consequences for the Scheme and for public health.

For these reasons, the Steering Committee considers these uses of Yellow Card data by independent researchers should normally not be permitted. The Steering Committee concludes that **requests for access to the entire database for research on 'signal detection', and/or for on-line access to the database, should be considered by the scientific committee and the Main REC.**

In the Steering Committee's view **access to the entire Yellow Card database should only be authorised in the most exceptional circumstances, and then under stringent**

**conditions. These would govern the proposed uses of the data and other conditions that the scientific committee considered appropriate after detailed discussions with the researcher.**

**Requests for on-line access should be subject to similar conditions but, if authorised by the scientific committee and Main REC, should be subject to a time lag.** This delay is necessary to enable MHRA to take any necessary regulatory action and to allow time for any information that is subject to the Data Protection Act 1998 to be removed.

### **3.10.6 Requests from researchers to contact reporters**

The reporter is the only person who can put a researcher in contact with a patient about whom a Yellow Card has been submitted. For research studies that involve consent of the patient and have been approved by the scientific committee and Main REC, the Steering Committee recommends that the MHRA should first contact the reporter, section 3.8.2. This route will reduce the risk of the identity of the reporter and patient being disclosed without consent.

To avoid overloading individual reporters, it would be good practice for MHRA to place a limit on the number of research requests sent to an individual reporter at any one time. Similarly, the reporter will be best placed to ensure that a particular patient is not overburdened with requests from researchers. The reporter is also best placed to decide how many times an 'interesting patient' should be asked to co-operate in a research project.

## **3.11 LEGAL AND OPERATIONAL ISSUES**

This section provides details which, for brevity, were not discussed in earlier sections of this chapter but which the Steering Committee took into account in formulating their conclusions and recommendations.

### **3.11.1 Data protection and confidentiality**

The Data Protection Act applies to data from which it is possible to identify a living individual (personal data). Since September 2000, to comply with the Data Protection Act 1998 and professional guidance, reporters no longer include the patient's name and date of birth on Yellow Cards (section 1.4.6). Instead, the reporter records only the patient's initials, age and a personal identification number, for example a practice or hospital number. A patient identifier, known only to the reporter, is needed in case follow-up information is requested by the MHRA; this procedure prevents the MHRA from identifying the patient.

The MHRA's legal advice is that, provided a patient cannot be traced from the anonymised Yellow Card data, the reporter is the data controller of the patient's personal data as defined in the Act. In this situation, the MHRA is not the data controller.

Yellow Cards still include the name and address of the reporter, and for these data the MHRA would bear the responsibility if a reporter's name or address was to be disclosed to a third party without consent. Disclosure without consent would deter reporters from submitting Yellow Cards. Data Protection and potential harm to the Scheme are the reasons for the Steering Committee's conclusions;

- 'that disclosure of details (of the reporter to a researcher) is not acceptable unless the reporter has agreed', section 3.4.1.
- 'It should be the MHRA's responsibility to ask the reporter if they consent to their details being passed to the researcher', section 3.4.1.

### **3.11.2 Ownership and legal provisions that affect the release of Yellow Card data**

While reporters submit the Yellow Card data and are the data controllers, the reports are collated and analysed by the MHRA for the CSM. Legal advice to the MHRA is that the Secretary of State 'owns' the Yellow Card data.

In addition to the Data Protection Act, the MHRA follows the Code of Practice on Access to Government Information. The Code commits all Government departments and agencies to the release of information upon request unless that information is covered by exemptions. Exemptions on personal and commercial confidentiality are relevant to the release of Yellow Card data.

In January 2005 the Freedom of Information (FOI) Act will come into effect. Until that date MHRA has to take account of the limitations on disclosure imposed by Section 118 of the Medicines Act. (In practice, MHRA has pragmatically interpreted its responsibilities and has not relied on section 118 as a sole justification for withholding information.) This anomaly will end with implementation of the FOI Act, as Ministers have agreed that Section 118 will be repealed.

### **3.11.3 Section 60 of the Health and Social Care Act 2001**

During this review, the Department of Health undertook a consultation on Section 60 of the Health and Social Care Act 2001 about the acceptability of patient identifiable data being processed without consent for a number of essential NHS activities. The data in the Yellow Card Scheme are anonymised. Notwithstanding this, the regulations made under Section 60 (The Health Service (Control of Patient Information) Regulations 2002 SI No 1483) expressly permit the processing of information for monitoring and managing adverse reactions to vaccines and medicines. In these circumstances, the Patient Information Advisory Group (PIAG) would be very unlikely to propose that Yellow Card data should be included under Section 60.

The Steering Committee's recommendation 'MHRA should make available the maximum amount of data', section 3.4.1, anticipates these legal changes. The Implementation of the FOI Act in 2005 should not affect the release of Yellow Card data for research through the mechanisms proposed in sections 3.4 and 3.7 of this chapter. The Steering Committee concludes that **the recommendations in this Review do not require any change to the Medicines Act or to subsidiary legislation.**

#### **3.11.4 European Legislation: Directive 2001/83/EC**

European legislation may in future affect the release of Yellow Card data. In particular, the modifications to Council Regulation 2309/93 on the centralised procedure and the EMEA and Directive 2001/83/EC, establish a Community code on medicinal products for human use. This new legislation requires the pharmaceutical industry and competent authorities (in the UK the competent authority is the MHRA) to introduce electronic exchange of ADR reports to the central pharmacovigilance database (EudraVigilance) held at the EMEA.

Another significant change will be the dissemination of information on ADRs, initially for centrally authorised products, to Member States, healthcare professionals and the public. This will be provided through a publicly accessible database.

The European Commission has not yet decided on the level of access which will be allowed. To ensure the confidentiality of personal data, as required by the Data Protection Act, the **MHRA has proposed only to submit for EudraVigilance the age group and sex of the patient and the country and qualifications of the reporter.** Although the final policy decision remains to be made, the Steering Committee **strongly endorses this approach as it will protect the anonymity of the patient and identification of the reporter.**

#### **3.11.5 Fees, costs and charges**

Any Yellow Card research that involves the patient or obtaining the patient's consent will inevitably have implications for the reporter, in terms of time and effort, for the benefit of the researcher. When a reporter agrees to speak to a patient, the reporter will first need to recall the patient to discuss and explain the proposed research and to ask for the patient's consent.

Stakeholders noted that pressure of work has deterred some reporters who give this as their reason for not submitting Yellow Cards. Requests addressed to reporters asking them to follow up patients for Yellow Card research purposes would be a further disincentive. Unless the Yellow Card research system includes some tangible recognition of the additional work undertaken by reporters who agree to contact and explain research to their patients, some reporters are unlikely to help. Others might even decide to cease submitting Yellow Cards.



'If further information or a sample for genetic testing is required following the initial report then in order to encourage continued reporting a fee will need to be paid to the reporter in providing that information and seeking the relevant consent.' Association of the British Pharmaceutical Industry (Annex I).

'When a reporter (usually, in this case, a GP) is required (with the permission of the patient) to undertake further work to produce a report or conduct further examinations or investigations, then an appropriate fee should be paid. The patient should be aware that a fee is being paid.' Royal College of General Practitioners (Annex I).

One stakeholder detailed the reimbursement procedures that occur in the EUDRAGENE<sup>24</sup> project as an example:

'Doctors are reimbursed for this extra work at a standard rate. If the doctor who has reported a suspected ADR is requested to collect a blood sample and to send it to the laboratory, this also is reimbursed.' Professor Paul McKeigue (London School of Hygiene and Tropical Medicine) (Annex I).

To avoid harming the Scheme and to facilitate Yellow Card research, the Steering Committee recommends **that reimbursement of expenses should be made to reporters who assist in research based on Yellow Cards for the time and effort needed to contact a patient and to obtain the patient's consent.** The fee would provide appropriate reimbursement and recognise the reporter's contribution to the research.

It should be emphasised that such fees should be paid only to reporters who are asked to contact a patient about Yellow Card research. **No fee should be paid when the MHRA asks a reporter for further details because the initial Yellow Card has been submitted incomplete or more clinical detail is needed before the significance of the report can be assessed.**

The Steering Committee recognises that payment of a fee for their involvement in Yellow Card research will not benefit or encourage the reporting of ADRs by health professionals who had not been the initial prescribers.

Some of the Steering Committee's recommendations will have cost implications for the MHRA. Examples are the operation and servicing of the scientific committee or the additional MHRA staff time needed for routine publication of Category I data. The MHRA will need finance to operate the additional purposes of the Scheme set out in this report.

The MHRA is a Trading Fund and as such is required to cover its costs. MHRA's income is derived from fees paid by the pharmaceutical industry. The Yellow Card system is currently

---

24 <http://www.genomica.net/farmagenomica/ricerca/EUDRAGEN.htm>

financed through the Trading Fund arrangements, but the industry may resist the Fund being used to introduce and finance new features in the Yellow Card Scheme.

*'We believe that any costs involved in obtaining data should be borne by the person or body requesting the data. If the system is funded by the MHRA with a nominal fee to researchers, this will have adverse financial consequences for industry as the Medicines Section of the MHRA is fully funded through fees from pharmaceutical companies. A subscription system might be appropriate for regular users.'* Association of the British Pharmaceutical Industry (Annex I).

Historically, the MHRA has not charged health professionals or patients for data requested but the Code referred to in section 3.11.2 and the FOI Act both enable MHRA, and other public bodies, to charge for information provided on request.

There is a risk that any charges imposed for access to Yellow Card data could be portrayed as MHRA 'selling' data that had been voluntarily provided for public benefit. This risk has to be balanced against the public health benefits from the results of Yellow Card research that follow from wider access to this unique database.

The Steering Committee **recommends that any changes introduced to the Scheme should be cost neutral to the MHRA. The collection, collation, analysis, publication and dissemination of Yellow Card data that are required by UK and European law, should continue to be supported through the Trading Fund arrangements.**

The Steering Committee **recommends the introduction of a scale of charges for research access to the Yellow Card data.** The charges would finance the administration of the new system and reimburse reporters. **The charging arrangements should be organised centrally by the MHRA through the scientific committee's secretariat.** This recommendation complies with the Government's policy on cost recovery by Government departments and agencies.

The Steering Committee also considered whether the scale of charges should be uniform or related to the position of the individual or organisation requesting the data. If the level of fees were too high, the data might be affordable only to investigators who have commercial sponsorship, and become inaccessible to academic researchers and individual health professionals. In view of the many collaborations between researchers and research sponsors, a two-tier scale of charges would, in practice, be difficult to enforce.

The views of stakeholders varied:

*'Any individual requiring access to yellow card data will be required to pay for it, in order to cover the costs of the MHRA. This type of charging is already in place for the use of GPRD. However, it is important that the costs are not so high that they impair any research efforts. The cost should be reasonable.'* Professor Munir Pirmohamed (SCOP member, RMC head) (Annex I).

*'In view of the importance of research into adverse reactions to relieve the extent of the burden, we would urge that any charges in respect of access for publicly-funded research or NHS should be minimal.'* Department of Health (Annex I).

*'Increased access will create increased work for MHRA and the Agency should be able to charge fees for this work, along the lines (say) of those charged for GPRD access. Some differentiation might be made between non-profit and profit-making bodies.'* Dr Ross Taylor (Annex I).

*'It should be possible toe (sic) establish some sort of sliding scale depending on the position of the person wanting to make use of the data and the likely benefit to the public good of the results.'* Professor Jenny Hunt (SCOP member) (Annex I).

*'In our view wider access would be for the purpose of strengthening the Scheme and improving public health so it should be publicly funded.'* Mind (Annex I).

The Steering Committee **recommends a single scale of charges for access to Yellow Card data that should apply uniformly to all organisations and individuals who receive Yellow Card data. The scale should be related to the amount of data provided and the work entailed in its preparation.** It remains desirable that **charges for access should be kept as low as possible** so that Yellow Card data is affordable by individual researchers and health professionals.

### **3.12 PATIENT REPORTING**

The Yellow Card Scheme does not obtain the patient's own perspective on ADRs. This is an important aspect that could be rectified through the introduction of direct patient reporting.

The MHRA and CSM have already considered the introduction of patient reporting, and there is an ongoing indirect patient reporting pilot scheme via the South East London NHS Direct call centre in Beckenham. This study involves reporting of patients' experiences of ADRs by nurses via NHS Direct (section 1.4.5 (iv)). The results of this pilot study have been disappointing.

The major criticism of the pilot study is that it is indirect patient reporting of nurses' interpretation of the patients' experiences. Stakeholders representing patients prefer a way for the patient to provide their own account of their experience.

*'The present pilot scheme heralded as "patients can now directly report adverse reactions" is misleading as patients can only report to NHS Direct. Therefore this system relies on a nurse deciding whether or not to report to the MHRA/CSM and the only difference is that patients report to a nurse as opposed to a doctor.'* Insulin Dependent Diabetes Trust (Annex I).

*'... qualitative comments, taken directly from patients, in their own words, and submitting these together with the yellow card, would add considerable value to the quality of information available on drug side effects.'* Consumers' Association (Annex I).

The Government's policy is to give patients greater choice over decisions affecting their health. As a part of this strategy, the number of drugs that have been moved to OTC status has risen in recent years. At the same time, many patients using IT and the internet, have done their own research on their illnesses and appropriate medicines that may be available. The Scheme will benefit from the direct input of patients about their own experience of side effects. Patients' experiences could identify ADRs not previously reported and/or specific features of ADRs that health professionals had not reported. For example, it was a letter from a patient that first identified a drug safety signal of a serious ADR from a herbal medicine. Patient reporting would increase awareness of the Scheme and lead to improved reporting rates by health professionals.

Most stakeholders supported the principle of direct patient reporting.

*'... patients should have the opportunity to contribute data using the yellow card system for medicines that have been obtained over the counter. Pharmacists are ideally placed to promote this and could actively encourage patients to send in appropriate data. This is complementary to the ethos of patient empowerment that is espoused within the "Expert Patient" (DoH, 2001).'* Association for Nurse Prescribing (Annex I).

However, other stakeholders were not in favour and had concerns about the value patient reporting would add.

*'We do not (sic) think that direct patient reporting will provide great assistance within the scheme because of excessive noise, bias and the effects of pressure groups.'* Scottish Medicines Consortium (Annex I).

*'I do not think that direct patient reporting will provide much help for the following reasons:*

- Noise due to non-severe, non-serious or poorly described reports
- Overload of the system and dilution of staff input
- Biased reporting by consumers with preconceived notions of the bad effects of medicines
- Stimulated reporting related to pressure groups e.g MMR or SSRI'. Dr Keith Beard (SCOP member) (Annex I).

Reservations were also expressed on how this should be organised. The Steering Committee considers that indirect reporting of patients' experiences is insufficient to give patients the opportunity to inform MHRA of their experiences. There is good evidence

that **in some situations, important features of ADRs have not been reported and an indirect patient reporting system can only provide the reporter's interpretation of the patient's symptoms.**

The Steering Committee **recommends that a direct patient reporting system should be introduced.** This should be via a mechanism through which patients could themselves report ADRs which they consider were due to medicines, irrespective of whether the prescriber has reported the ADR or agrees with the patient's view.

### **3.12.1 Practical concerns about a direct patient reporting system**

The main concerns of stakeholders who do not support direct patient reporting, are:

- (i) too many reports of minor and well-known ADRs could flood the system and create so much 'background noise' that identification of new drug safety issues would become more difficult;
- (ii) there would be much greater duplication of ADR reports;
- (iii) patient reports might be used by campaigning groups to create a signal;
- (iv) there would be resource implications for MHRA and patient reports could divert attention from more important ADR reports from health professionals.

The Steering Committee recognises these concerns but do not consider they outweigh the benefits of a robust and validated method for collecting direct patient reports. Further exploration of different systems will be needed. Both data sets could be used to complement one another. The Steering Committee **recommends that systems for direct patient reporting of ADRs should be piloted.**

*'In considering the potential for direct reporting for consumers, it would be worthwhile investigating a number of different approaches as pilot studies and evaluating these.'* Consumers' Association (Annex I).

Stakeholders' concerns about overload to the existing system and an abundance of reports of minor ADRs could be avoided by keeping patient reports separate. The Steering Committee **recommends keeping patient reports separate from those from health professionals until pilot investigations have identified the best way forward.**

A practical suggestion about patient reports made by stakeholders, to avoid duplication and to link a patient's report to the reporter's Yellow Card, was a tear-off slip bearing the Card reference number for the patient to attach or quote in the patient report.

### 3.13 STRENGTHENING OF THE YELLOW CARD SCHEME

#### 3.13.1 Support for the Yellow Card Scheme

The strong support for the Scheme from a wide range of stakeholders is described in section 3.1. Professional stakeholders also commented that some of their colleagues are barely aware of the Scheme, while other potential reporters do not know which ADRs they should report or, in some cases, how to go about reporting.

*'The current schemed (sic) would be strengthened if the rate of reporting were increased. The rate of reporting might be increased if there was more frequent and more detailed feedback to potential contributors.'* ARC Epidemiology Unit (Annex I).

Stakeholders added that the Scheme and its purposes are largely unknown to patients and the public. Stakeholders agree on the **need for action by the MHRA to strengthen the Scheme, and to raise awareness of it among health professionals and the public. Potential reporters should be better informed of how they can contribute to it.**

To realise these objectives a **communication strategy** will be needed. The strategy will have the dual purpose of raising the profile of the Scheme and publicising the changes implemented following this Review. In the longer term, **an ongoing communication programme will be required** to maintain the higher profile for the Scheme. This should raise reporting rates and thereby enhance signal detection and the Scheme's potential use in research. These objectives reinforce the Steering Committee's recommendation, that *'a comprehensive communication strategy for health professionals and for the public will be required to provide a clear understanding of the reasons for any changes to the Scheme and purposes for which Yellow Card data may be made available'* (section 3.1).

#### 3.13.2 Components of the communication strategy

The primary purpose of the strategy will be to provide better information and education about the Scheme for the health professions, patients and the public. There are many different routes that could be used in the strategy.

**The Scheme and the reasons for it should receive much greater emphasis during the clinical training** of medical students in particular, but also of all other health professionals who have prescribing responsibilities.

Similarly, as part of continuing professional education, trainers should test the junior doctors' knowledge of the Scheme, and **greater emphasis should be placed on the professional duty of all prescribers to report ADRs.**

In some hospitals it is not clear who is responsible for reporting ADRs to the Scheme. There is a risk that in hospital practice ADRs are not reported because of this uncertainty.

**A clear policy should be developed by each Trust to clarify where this responsibility lies.**

**The availability of the Yellow Card on the internet<sup>25</sup> should be advertised, and electronic reporting promoted** as the preferred and faster method of submitting a Yellow Card. **Reporters should be encouraged to use this method.**

**Computer programmes, including those in wide use in General Practice, could include prompts to encourage prescribers to pause and consider if a Yellow Card should be submitted.**

**Information technology (IT) could be harnessed to enhance reporting** through improvements in the community pharmacists linkages to the NHSnet, electronic linkages between GPs and community pharmacists via the Integrated Care Record Service (ICRS), and the development of single electronic patient records.

**The Scheme could be promoted to patients through the inclusion of a contact website address in patient information leaflets (PILs) supplied with medicines.** This way of informing patients about the Scheme will be even more relevant if the recommendations for patient reporting are implemented.

Feedback from the Scheme to reporters can be very effective in stimulating their interest and in encouraging further reports. In this context, **the timeliness and content of the CSM's drug safety bulletin 'Current Problems in Pharmacovigilance' should be reconsidered.**

For patients and the public, **posters and leaflets about the Scheme could be provided for display in surgeries and hospitals.** This would emphasise to the public the presumption that reporters will submit Yellow Cards when ADRs are suspected.

*'For wider access especially it is very important that patients are made aware of the way in which their data might be used. We hope that information in the surgery might be the way forward.'*  
Department of Health and MRC (Annex I).

The MHRA should identify ways to enable those with an interest in emerging ADRs to obtain up-to-date information.

For reporters and potential reporters, **the MHRA should develop a communication strategy to improve professional and public education and provision of information about the Yellow Card Scheme. This must clarify:**

---

<sup>25</sup> <http://www.yellowcard.gov.uk>

- the types of ADRs that should always be reported;
- the role of Regional Monitoring Centres;
- local feedback to reporters where there is no RMC;
- how all those with an interest in emerging ADRs can obtain up-to-date information.

### 3.13.3 Clarification of which ADRs should be reported

Stakeholders have asked for greater clarity about which ADRs should be reported to the Scheme. Currently, MHRA requests all ADRs associated with black triangle (▼) drugs and 'serious' ADRs associated with older products. This will not change, but it was noted that stakeholders want a clearer definition of 'serious' ADRs. Stakeholders also suggested some other products and uses of medicines which might be given a higher profile in the Scheme. These include ADRs from:

- (i) products whose legal status has been recently changed. As medicines become more widely available, a change in legal status either from Prescription Only Medicine (POM) to the Pharmacy (P) medicine list or Pharmacy medicine to the General Sales List (GSL), could produce different ADRs experienced among a wider range of patients;
- (ii) off label use of licensed products;
- (iii) use of all unlicensed medicines and drugs;
- (iv) ADRs that are not mentioned in the SPC or PIL.

The Steering Committee agrees with stakeholders who commented that **it is essential for the Scheme to maintain its focus upon serious ADRs and black triangle (▼) products; but greater clarity is required about the meaning of 'serious' and which other ADRs should be reported.**

**To improve the Scheme's capacity to identify ADRs, MHRA should consider what emphasis in future should be given on receiving Yellow Card reports on:**

- off label use of licensed products;
- products whose legal status has changed;
- ADRs that are not mentioned in SPCs and PILs.

The Steering Committee also agrees with **stakeholders who were concerned that the Scheme should not become overloaded with too many reports of minor and/or well-recognised ADRs that are already well documented.** This will be important in the context of patient reports.



### 3.13.4 Reporting ADRs

Stakeholders have raised two separate questions about the reporting of ADRs:

#### (i) Parallel reporting systems

Some stakeholders drew attention to parallel systems for reporting incidents, adverse events and ADRs to other Government bodies such as the National Patient Safety Agency (NPSA), and the Health Protection Agency (HPA), and to non-governmental organisations through Prescription Event Monitoring (PEM) by the Drug Safety Research Unit (DSRU). More recently, a further possibility is the collection of reports by the EMEA.

Faced with reporting systems for different purposes, it is not surprising that some health professionals have asked whether all ADRs involving medicines should be reported only to the MHRA, or are there circumstances where an ADR should be reported to another Government agency or to both agencies.

The Medicines Act places on MHRA the responsibility for ensuring that medicines meet appropriate standards of safety, quality and efficacy. To enable the MHRA to fulfil its legal responsibilities as the UK Competent Authority and to inform the CSM and Ministers of any findings that impact on the safety of medicines, the Steering Committee is convinced that the **MHRA should continue to collect, collate and analyse all Yellow Cards reporting suspected ADRs associated with medicines** (section 1.2).

There may, however, be particular circumstances when an incident involving a medicine should also be reported to another Government agency. To clarify when an ADR should be reported both to MHRA and another Government agency, the Steering Committee **recommends that the MHRA should work jointly with the NPSA and HPA to prepare joint policy statements.**

*‘Appropriate sharing of data between the MHRA and the NPSA on ADRs and adverse events is important.’* British Pharmacological Society (Annex I).

These statements would provide health professionals with a clear understanding of the responsibilities of each agency and clarify if there are circumstances when an ADR involving a medicine should be reported to the MHRA and to another agency. The preparation of such statements would also avoid unnecessary duplication of effort and strengthen the MHRA’s working relationships with the NPSA and HPA.

The statements could be publicised to all health professionals and to the NHS as part of the communication strategy.

## (ii) The routing of Yellow Card reports

This question affects only those parts of the UK where Regional Monitoring Centres (RMCs) are in operation. In these areas, the practice has developed for many reporters to send Yellow Cards to the RMC for onward transmission to the MHRA while other reporters continue to send Yellow Cards direct to the MHRA.

The RMCs correctly point out that they cannot carry out their important monitoring, education and information functions if they do not have access to all the Yellow Cards from the areas they cover.

The RMCs have expressed a preference for all Yellow Cards from their respective areas to be routed through them, but these centres only operate in parts of the UK. One of the conclusions of this Review is that **the Yellow Card system should continue as a single scheme covering the whole of the UK**. A mixed reporting system with different reporting procedures in different places would not only conflict with the principle of a single system, but would also confuse reporters who move from an RMC area to one without, or in the other direction.

Two other factors affect the route for Yellow Card reports. The Medicines Act places responsibilities on the MHRA rather than the RMCs, and the Steering Committee has also recommended that on-line Yellow Card reporting should, in this electronic age, be encouraged, section 3.13.2. On-line reports should preferably be addressed to a single mailbox.

Taking account of all these factors, the Steering Committee **proposes that all Yellow Card reports (paper and electronic) should be sent by the reporter to the MHRA, and that all Cards received by the MHRA from areas where RMCs are in operation should be copied as soon as possible to the relevant RMC**. Reports received electronically can be transmitted immediately while those in hard copy should be sent to the RMC as soon as the postcode of origin has been coded. The IT processing arrangements within the MHRA was not part of the Review's remit.

**Reporters in areas covered by the RMCs should be made aware of their functions, and that information from Yellow Cards within each RMC's geographical area will be shared between the MHRA and the RMC in order to increase local reporting rates.**

What is important is that the RMCs receive all reports from their areas and minimise the chance of confusing reporters about where to report ADRs.

Two members of the Steering Committee did not agree with the proposed routing of all Yellow Cards via the MHRA. They believed that the current higher levels of reporting and

successful follow-up from RMC areas were largely attributable to the direct reporting to, and follow up by, the local centre. Methods need to be explored to continue local identification with the dataset within a comprehensive UK system, with minimum duplication of workload.

### 3.13.5 Regional Monitoring Centres

The background and activities of these centres were described in section 1.4.3. The success of the centres in raising local ADR reporting rates and their experience in professional education and feedback for reporters, illustrate different features that should form part of the communication strategy.

A number of stakeholders support the role of the RMCs and suggest that they could be used to increase reporting rates, improve education about the Scheme and conduct pilot studies of patient reporting.

*‘The British Pharmacological Society believes that importance of the Regional Monitoring Centres should be emphasized and their role supported and enhanced.’* British Pharmacological Society (Annex I).

*‘The possibility that RMCs might support local NHS Direct centres in their role in facilitating patient reporting should also be explored.’* British Pharmacological Society (Annex I).

#### (i) Professional education

**The Yellow Card Scheme should be included in the training of all health professionals whether they prescribe or not. However, for prescribing health professionals, the Scheme and its importance should also be included as part of their continuing professional development (CPD).**

Some stakeholders supported the introduction of Continuing Medical Education (CME) points;

*‘Healthy (sic) professionals should receive more credit for making reports. While we are not in favour of the introduction of a fee for making a report, some credit should be provided in another way, e.g CME points.’* British Pharmacological Society (Annex I).

The Regional Monitoring Centres have been notably successful in raising the Scheme’s profile and in educating junior doctors, pharmacists and nurses about which ADRs to report. RMCs have done this through targeting local reporter groups with success and increased ADR reporting rates have followed. Providing professional education is an uphill task as the programme has to be repeated for each new generation of reporters.

The Steering Committee commends the **targeted professional education, developed by the RMCs. These provide models that could be introduced in other parts of the UK**, as part of the communication strategy. The Committee recognises that professional education programmes require financial resources and the commitment of the staff involved, and the RMCs have shown how important these factors are to success.

(ii) **Feedback to reporters**

The RMCs have used their analyses of Yellow Card data to provide regular feedback to reporters. Use of data on local patterns of reporting is essential for this process and feedback to reporters should be timely and at regular intervals. Feedback on reporting patterns and rates can and should be incorporated into other educational programmes. **The RMCs' experience in providing feedback provides a further role model. The RMCs should be more closely integrated in the Scheme. As part of the communication strategy the type of feedback provided by RMCs should be tried in other places to raise reporting rates.**

(iii) **Research and pilot studies**

**The RMCs have a potential research role, as their success in introducing new reporter groups has demonstrated. The Centres are well placed to design and facilitate pilot studies arising from this Review.**

(iv) **Healthcare in Scotland and Wales**

**The RMCs in Edinburgh and Cardiff have, respectively, an important role to provide the Scottish Parliament and Welsh Assembly with information relevant to their responsibilities.**

(v) **Other features of the RMCs and their work**

The RMCs also undertake other functions. The Centres provide, or are integrated with, Regional Drug Information Centres; as such, they provide a 'one stop shop' which clinicians and reporters can consult on any question affecting the safety of medicines. These functions, while beyond the scope of the Yellow Card Scheme, bring benefits to it. The Steering Committee **commends the work of the RMCs.**

The relationship between the MHRA and the RMCs appears rather too informal. Under the present arrangements, it is not clear where responsibility lies or decisions are taken, including feedback to the reporter. In commending the educational role of the RMCs and their success in raising reporting rates, the Steering Committee **recommends that the role of the RMCs should be clarified. A protocol should be agreed to define the relationship, respective responsibilities and working practices between the MHRA and the RMCs.** This will be for their mutual benefit.

There are a number of general principles and practical arrangements that should inform the work of the RMCs:

- **Yellow Card data should be freely shared between the MHRA and RMCs;**
- **RMCs should work to the same Standard Operating Procedures (SOPs) as the MHRA;**
- RMCs have been effective in **retrieving and acknowledging data from reporters** that was missing when a Yellow Card was first submitted. To avoid duplication of work, **this should continue but be subject to an agreed protocol;**
- **there should be agreement between the MHRA and the RMCs about their respective responsibilities.**

### 3.14 IMPLEMENTATION OF CHANGES

There are a number of ways, as described above, in which ADR reporting rates might be improved. The Steering Committee **recommends that, where appropriate, pilot studies should be undertaken to identify the best ways of raising ADR reporting rates and to inform and educate health professionals and patients about the Scheme. Direct patient reporting systems, as proposed by stakeholders, can also be tested through local pilot studies.**

### 3.15 OTHER ISSUES

During the consultation some other issues were raised which, after discussion, the Steering Committee does not recommend.

#### 3.15.1 An incentive payment scheme to encourage ADR reporting

One theoretical way to encourage Yellow Card reporting could be via the payment of a fee to reporters for every Yellow Card sent to the MHRA and CSM. This idea was discussed during the 1984 Expert Review of the Scheme. At that time the Review Group wrote, '*If the proposed payment were large, it might stimulate excess reporting of trivial reactions; if small, it would not be a spur to reporting and would be disproportionately expensive to administer*' (Annex J).

The Steering Committee agrees that the same logic applies today. Incentive payments would change the Scheme's fundamental practicalities. There would be both direct costs and administration costs and extra staff needed. There was virtually no support from stakeholders for an incentive payment. Indeed, several stakeholders are robustly opposed and believe that a doctor, or other reporter, has a professional responsibility to send in a Yellow Card when he suspects his patient experiences an ADR.

### **3.15.2 A legal requirement to report ADRs**

Some countries have legislation or other mandatory systems that seek to compel doctors to report ADRs. In practice, comparison of inter-country ADR reporting rates suggests that rates are no better in countries that have mandatory Schemes than those that do not (Hughes *et al*, 2002).

At first sight, a legal requirement on reporters to compel ADR reporting through the Scheme has some attraction, but the Scheme is there for reporters to draw attention to suspected, not proven, ADRs. It is difficult to see how a law could be effective if it required a reporter to report 'a suspicion'. How can failure to report a suspicion be proven? It would be too simple for any reporter to argue that he had no such suspicion.

The Steering Committee does not recommend a mandatory system because of the absence of any clear increase in reporting rates in countries that have these and the practical difficulties of enforcement.

### **3.15.3 Merger of the Yellow Card Scheme with the similar Scheme for medical devices**

The MHRA also runs a separate Scheme for health professionals to report adverse events resulting from medical equipment and devices. The Schemes have similar aims but different procedures. Although there are arguments for the MHRA to merge the two Schemes, in practice the data collected through the two are very different. Merger of the two Schemes was not advocated by any stakeholder during the course of this Review. The Steering Committee is satisfied that the collection of adverse incidents relating to medical devices and equipment by the MHRA should continue as a distinct and separate Scheme.

# 4 RECOMMENDATIONS

This chapter lists all the recommendations from the Review, including the main recommendations highlighted in the Summary.

## **Basic principles**

The Steering Committee strongly endorses the value and importance of the Yellow Card Scheme for public health and the benefit of patients. These were emphasised by stakeholders. The Committee also agrees with stakeholders that any changes to the Scheme must not harm it or deter reporters from submitting Yellow Cards (section 3.1).

To enable the MHRA to fulfil its legal responsibilities as the UK Competent Authority and inform the CSM and Ministers of any findings that impact on the safety of medicines, the MHRA should continue to collect, collate and analyse all Yellow Cards reporting *suspected* ADRs associated with medicines (section 3.13.4(i)).

The basic principles of the Scheme, as set out in Sir Derrick Dunlop's letters in 1964, should not be changed. Any new uses of Yellow Card data should strengthen the Scheme but must not put its future at risk (section 3.1).

Any amendments to the original principles of the Yellow Card Scheme must be subject to appropriate controls being in place; these should not detract from the Scheme's ability to fulfil its original purpose (section 3.1).

## **Access to data**

### **Release of data**

A recognised procedure for accessing Yellow Card data would avoid arguments over Freedom of Information (section 3.1.1).

The MHRA should open access to the Yellow Card database, and should maximise the release of data from the Scheme for independent research subject to appropriate safeguards (section 3.4.1).

The database cannot be used in studies to determine the incidence of particular ADRs as reporting may reflect a high public profile rather than real incidence. Any researcher or investigator using the Yellow Card database must be aware of these and other limitations of the data (section 3.2.1).

The Yellow Card Scheme should continue as a single scheme covering the whole of the UK (section 3.13.4 (ii)).

A comprehensive communication strategy for health professionals and for the public will be required to provide a clear understanding of the reasons for any changes to the Scheme and purposes for which Yellow Card data may be made available (section 3.1).

### **Freedom of Information; aggregated anonymised data sets**

The first category of Yellow Card data comprises aggregated anonymous non-identifiable data and excludes all patient and reporter details (section 3.4.1).

The MHRA should make available the maximum amount of data within this category through publication of data sets or in response to FOI requests (section 3.4.1).

Wherever possible, anonymised aggregated data should be regularly published on the MHRA website accompanied by guidance on interpretation. The frequency of updating would depend on the rate at which the data profile changes, but in considering the range of data placed on the website and the frequency of updating, the MHRA should bear in mind that feedback undoubtedly improves reporting rates. Other data sets that are not regularly published should be available on request, under FOI (section 3.4.1).

### **Scientific review of requests for data from individual Yellow Cards**

Scientific safeguards must be put in place to protect patient confidentiality and to ensure that data are only released for research and other purposes that have been independently evaluated (section 3.5).

Requests for data not subject to FOI and for data from individual Yellow Cards should be assessed by an independent scientific committee set up by the Licensing Authority to ensure that proposals for research using Yellow Card data are scientifically robust (section 3.5).

The second category of Yellow Card data, Category II, would include the information contained in individual Yellow Cards, but patient and reporter identifiable data would not be included (section 3.4.1).

The third level, Category III, would enable the person receiving the data to request from the reporter further information about the patient (section 3.4.1).



The scientific committee must have sole responsibility for evaluating the scientific merit of research proposals that would require the use of Categories II and III Yellow Card data. The MHRA should have an opportunity to offer comments but the scientific committee must be free to accept or discount these (section 3.10.2).

If research findings call in question the safety of a licensed medicine, the findings should be considered without delay by the CSM and MHRA (section 3.7.2).

The research applicant should be accountable to the scientific committee and be provided with clear terms and conditions setting out the purposes for which the Yellow Card has been released. These should include firm guidance on release of data to third parties and data storage conditions (section 3.10.2).

To manage straightforward research proposals that request Category II but not Category III data, the scientific committee should develop a set of criteria. Requests for Yellow Card data for proposals that satisfy these criteria could be released by the MHRA without the need for all Category II proposals to be considered by the scientific committee. The committee should be informed of all such data released by the MHRA (section 3.10.2).

The scientific committee should publish the criteria and its other rules of procedure for data release. These criteria must not permit the release of reporter or patient identifiers (section 3.10.2).

Access to the database should be managed through a single central system. There should be no by-pass mechanisms or exemptions. The scientific committee should consider all proposals under the same set of rules, irrespective of their origin (section 3.7.1).

Any research collaboration between the MHRA and researchers would also be subject to the same criteria (section 3.7.1).

An appeal mechanism should be available for research applicants whose requests for Yellow Card data are refused, but limited to those who can show that they have good reasons to challenge the scientific committee's decision. The appeal procedure could be similar to that already in place for the MHRA's statutory committees (section 3.10.2).

### **Ethics Review**

Where appraisal of ethical issues is required (all Category III and selected Category II), this should be carried out separately and independently of scientific appraisal and the appraisal should be undertaken through the COREC system (section 3.6).

A Main REC must be consulted about any proposed research that may involve access to a patient or procedures that require consent, including personal information about the

patient known to the reporter, or other procedures that under normal conditions require ethical approval (section 3.6).

Scientific appraisal of a research proposal should precede ethical review (section 3.4.1).

The scientific committee and Main REC should not authorise the release of Yellow Card data for direct financial gain (section 3.10.4).

Independence of both the scientific and ethics committees from the MHRA and CSM is of great importance in order to avoid allegations of bias (section 3.6).

### **Audit**

Sir Derrick Dunlop's original promise must be honoured (section 3.9).

Provided the scientific committee and Main REC are satisfied that (i) a specific proposal complies with the Dunlop principles, and that (ii) the application is scientifically and ethically acceptable, there is no reason that would justify the arbitrary exclusion of proposals to the use of Yellow Card data for audit purposes (section 3.9).

### **Genetic and specialised research**

Any proposals for use of Yellow Card data for genetic research should be subject to the same scientific and ethical scrutiny as all other genetic research proposals. Therefore, genetic proposals should always be considered by the scientific committee and Main REC (section 3.3).

When the scientific committee has before it a research proposal that includes genetic or other specialised research, the committee must ensure that it has amongst its membership sufficient experience and/or expertise to assess a research proposal involving any aspects of genetics, or co-opt a person with appropriate experience. The same principle applies to other specialised research (section 3.3).

The ethical principles set out by the Human Genetics Commission must apply to all forms of genetic research (section 3.3).

The implications of any research for relatives should be considered by the scientific committee and Main REC (section 3.3).

### **Access to the entire database and on-line access**

Requests for access to the entire database for research on 'signal detection', and/or for on-line access to the database, should be considered by the scientific committee and the Main REC (section 3.10.5).

Access to the entire Yellow Card database should only be authorised in the most exceptional circumstances, and then under stringent conditions. These would govern the proposed uses of the data and other conditions that the scientific committee considered appropriate after detailed discussions with the researcher (section 3.10.5).

Requests for on-line access should be subject to similar conditions but, if authorised by the scientific committee and the Main REC, should be subject to a time lag (section 3.10.5).

### **Patient consent**

The Steering Committee recommends that current practice should continue. Health professionals should not be required to obtain the patient's consent before submitting an anonymous Yellow Card (section 3.8.1).

It would be good practice for the reporter to inform the patient that he is submitting, or has submitted, a Yellow Card (section 3.8.1).

The patient must provide fully informed consent for any use in research of their personal or identifiable information and, for obvious reasons, for their physical participation in research (section 3.8.2).

When consent is requested, the reporter will normally be in the best position to explain the research to the patient and then to ask for consent. If a patient refuses to give consent, that decision must have no influence on the patient's current or future clinical care (section 3.8.2).

When the reporter is neither the prescriber nor the patient's general practitioner, the reporter should pass the request for access to the patient's general practitioner who can then decide whether or not the patient should be asked to participate in further research (section 3.8.2).

When the scientific committee and Main REC authorise research that requires contact between the researcher and the reporter, the MHRA should act as an intermediary between them and the MHRA must make the initial contact with the reporter (section 3.8.2).

### **Publication of research findings**

All researchers should be contractually required to notify the MHRA, the scientific committee and the Main REC of their plans to publish or disseminate research findings based on Yellow Card data, and provide copies of any proposed publications or other forms of presentation. The MHRA should inform the relevant Marketing Authorisation Holders (MAHs). Notification, and pre-publication copies, of reports should be provided 28 days in advance (section 3.7.2).

### **Reimbursement of reporters' expenses and fees**

The collection, collation, analysis, publication and dissemination of Yellow Card data that are required by UK and European law should continue to be supported through the Trading Fund arrangements (section 3.11.5).

Any changes introduced to the Scheme should be cost neutral to the MHRA (section 3.11.5).

Reimbursement of expenses should be made to reporters who assist in research based on Yellow Cards for the time and effort needed to contact a patient and to obtain the patient's consent (section 3.11.5).

No fee should be paid when the MHRA asks a reporter for further details because the initial Yellow Card has been submitted incomplete or indicated the need for more clinical detail before the significance of the report can be assessed (section 3.11.5).

There should be a scale of charges for researchers accessing Yellow Card data that is not subject to FOI. This should be published on the MHRA website. The level of charges should relate to the volume of work involved (section 3.11.5).

These charges should apply uniformly to all organisations and individuals who receive Yellow Card data. It remains desirable that charges for access should be kept as low as possible so that Yellow Card data is affordable by individual researchers and health professionals (section 3.11.5).

The MHRA should set up an administrative system to manage the research procedures and the reimbursement of expenses. The charging arrangements should be organised centrally by the MHRA through the scientific committee's secretariat (section 3.11.5).

### **Strengthening the scheme**

It is essential for the Scheme to maintain its focus upon serious ADRs and black triangle (▼) products; but greater clarity is required about the meaning of 'serious' and which other ADRs should be reported. To improve the Scheme's capacity to identify ADRs, MHRA should consider what emphasis in future should be given on receiving Yellow Card reports on:

- off label use of licensed products;
- products whose legal status has changed;
- ADRs that are not mentioned in SPCs and PILs (section 3.13.3).

The Scheme and the reasons for it should receive much greater emphasis during the clinical training of all health professionals, whether they prescribe or not. In particular, information and professional education about the Scheme should be addressed to those involved in independent and supplementary prescribing during clinical training. For prescribing health professionals, it should also be included as part of their continuing professional development (CPD) (section 3.13.5(i)).

Greater emphasis should be placed on the professional duty of all prescribers to report ADRs (section 3.13.2).

The availability of the Yellow Card on the internet should be advertised and electronic reporting could be promoted. Reporters should be encouraged to use this method (section 3.13.2).

Computer programmes, including those in wide use in general practice, could include prompts to encourage prescribers to pause and consider if a Yellow Card should be submitted (section 3.13.2).

Information technology (IT) could be harnessed to enhance reporting through improvements in the community pharmacists' linkages to the NHSnet, electronic linkages between GPs and community pharmacists via the Integrated Care Record Service (ICRS) and the development of single electronic patient records (section 3.13.2).

The Scheme could be promoted to patients through the inclusion of a contact website address in PILs supplied with medicines (section 3.13.2).

For reporters and potential reporters, the MHRA should develop a communication strategy to improve professional and public education and provision of information about the Yellow Card Scheme. This must clarify:

- the types of ADRs that should always be reported;
- the role of Regional Monitoring Centres;
- local feedback to reporters where there is no RMC;
- how all those with an interest in emerging ADRs can obtain up-to-date information (section 3.13.2).

The timeliness and content of the CSM's drug safety bulletin '*Current Problems in Pharmacovigilance*' should be reconsidered (section 3.13.2).

Posters and leaflets about the Scheme could be provided for display in surgeries and hospitals (section 3.13.2).

A clear policy should be developed by each Trust to clarify who is responsible in their hospitals for reporting ADRs to the Scheme (section 3.13.2).

The MHRA should work jointly with other Government agencies, including the NPSA and HPA, to prepare joint policy statements to clarify when an ADR should be reported both to MHRA and another Government agency. The statements could be publicised to all health professionals and to the NHS as part of the communication strategy (section 3.13.4(i)).

### **Regional Monitoring Centres**

The RMCs should be more closely integrated in the Scheme. As part of the communication strategy the type of feedback provided by RMCs should be tried in other places to raise reporting rates (section 3.13.5(ii)).

The targeted professional education developed by the RMCs could be introduced in other parts of the UK as part of the communication strategy (section 3.13.5(i)).

All Yellow Card reports (paper and electronic) should be sent by the reporter to the MHRA. All Cards received by the MHRA from areas where RMCs are in operation, should be copied as soon as possible to the relevant RMC (section 3.13.4(ii)).

Reporters in areas covered by the RMCs should be made aware of their functions, and that information from Yellow Cards within each RMC's geographical area will be shared between the MHRA and the RMC in order to increase local reporting rates (section 3.13.4(ii)).

RMCs should work to the same Standard Operating Procedures (SOPs) as the MHRA (section 3.13.5(v)).

To avoid duplication of work, the RMCs should continue to retrieve and acknowledge data from reporters that was missing when a Yellow Card was first submitted, but be subject to an agreed protocol (section 3.13.5(v)).

The role of the RMCs should be clarified. A protocol should be agreed to define the relationship, respective responsibilities and working practices between the MHRA and the RMCs (section 3.13.5(v)).

### **Patient reporting**

A system should be set up for patients to report ADRs directly to the MHRA (section 3.12).

Indirect reporting is insufficient to give patients the opportunity to inform MHRA of their experiences. There is good evidence that, in some situations, important features of ADRs have not been reported, as an indirect system can only provide the reporter's interpretation of the patient's experience (section 3.12).

Different approaches to managing patient reporting should be tried but, initially, patient reports should be kept separate from those of health professionals through a parallel system until experience indicates the best method of linking patient and Yellow Card reports to the same ADR (section 3.12.1).

### **Implementation of changes**

Pilot studies should be undertaken to identify the best ways of raising ADR reporting rates and to inform and educate health professionals and patients about the Scheme. Direct patient reporting systems should be tested through local pilot studies (section 3.14).

The Steering Committee does not consider, or recommend, any changes to the Medicines Act are needed to implement the recommendations of this Review (section 3.11.3).

# BIBLIOGRAPHY AND REFERENCES

Anon. Extension of the Yellow Card Scheme to unlicensed herbal remedies. *Current Problems in Pharmacovigilance* 1996 **22**: 10.

Anon. Pharmacists' adverse drug reaction reporting to start on April 1. *Pharmacol J* 1997a **258**: 330–331.

Anon. Electronic yellow card in GP computer prescribing systems. *Current Problems in Pharmacovigilance* 1997b **23**: 10.

Anon. HIV adverse drug reactions reporting scheme. *Current Problems in Pharmacovigilance* 1998a **24**: 3.

Anon. HIV ADR reporting scheme. The first seven months. *HIV ADR Reporting Scheme News* August 1998b 1.

Anon. 'Yellow card' reporting now allowed for all community pharmacists. *Pharmacol J* 1999 **263**: 776.

Anon. Reminder: St John's wort (*Hypericum perforatum*) interactions. *Current Problems in Pharmacovigilance* 2000a **26**: 6–7.

Anon. Updated 'yellow card' launched. *Pharmacol J* 2000b **265**: 387.

Anon. Yellow card updated to protect privacy. *Scrip* 2000c **2575**: 6.

Bateman D N, Sanders G L S and Rawlins M D. Attitudes to adverse drug reaction reporting in the Northern Region. *Br J Clin Pharmacol* 1992 **34**: 421–426.

Belton K J and The European Pharmacovigilance Research Group. Attitude survey of adverse drug-reaction reporting by health care professionals across the European Union. The European Pharmacovigilance Research Group. *Eur J Clin Pharmacol* 1997 **52** (6): 423–7.



Belton K J, Lewis S C, Payne S, Rawlins M D and Wood S M. Attitudinal survey of adverse drug reaction reporting by medical practitioners in the United Kingdom. *Br J Clin Pharmacol* 1995 **39**: 223–226.

Butler N. Perinatal Mortality Survey/National Child Development Study 1958;  
<http://www.dataarchive.ac.uk>

Cave E, Holm S, Milgram and Tuskegee. Paradigm Research Projects in Bioethics. *Health Care Analysis* March 2003 **11** (Issue 1): 27–40.

Chamberlain R and Chamberlain G V P. *British Cohort Study 1970* Heinemann, London.

Davis S, Coulson R A and Wood S M. Adverse drug reaction reporting by hospital pharmacists: the first year. *Pharmacol J* 1999 **262**: 366–367.

Davis S and Raine J. Spontaneous reporting – UK. In: *Pharmacovigilance* Mann R and Andrews E ed. 2002 John Wiley and Sons Ltd.

Douglas J W B. *Maternity in Great Britain 1948* Oxford University Press.

General Medical Council. Confidentiality: protecting and providing information. June 2000 [www.gmc-uk.org/standards/](http://www.gmc-uk.org/standards/)

Griffin J P and Webber J C P. Voluntary systems of adverse reaction reporting. In: Griffin, J P. ed., *Medicines: regulation, research and Risk*, 2nd ed. 1992; Belfast: the Queen's University.

Griffin J P. Survey of the spontaneous adverse reaction reports schemes in fifteen countries. *Br J Clin Pharmacol* 1986 **22**: 83S–100S.

Houghton J E, Pinto Pereira L M, Woods F J, Richens A and Routledge P A. The Welsh adverse drug reactions scheme: experience of a UK regional monitoring centre. *Adverse Drug React Toxicol Rev* 1996 **15**: 93–107.

Hughes M L, Whittlesea C M C and Luscombe D K. Review of National spontaneous reporting schemes. *Adv Drug React Toxicol Rev* 2002 **21** (4): 231–241.

Lee A, Bateman D N, Edwards C, Smith J M and Rawlins M D. Reporting of adverse drug reactions by hospital pharmacists: pilot scheme. *BMJ* 1997 Aug 30; **315** (7107): 519.

Medicines Control Agency. *Annual Report and Accounts 2002/03* Her Majesty's Stationery Office, London, July 2003.

Ministry of Health, Scottish Home and Health Departments. *Safety of Drugs – Final Report of the Joint Sub-Committee of the Standing Medical Advisory Committees*. Her Majesty's Stationery Office, London, 1963.

Morrison-Griffiths S. Adverse drug reaction reporting by nurses. M Phil Thesis 2000, University of Liverpool.

Morrison-Griffiths S, Walley T J, Park B K, Breckenridge A M and Pirmohamed M. Reporting of adverse drug reaction by nurses. *Lancet* 2003 Apr 19; **361** (9366): 1347–1348.

Penn R G. Iatrogenic disease: an historical survey of adverse reactions before thalidomide. Chapter 2 In: *Iatrogenic Diseases* D'Arcy, P F and Griffin, J P ed. Oxford University Press, Oxford 1986, pp 14–21.

Shah D *et al.* Toxicological problems resulting from exposure to traditional medicines and supplements. Sept. 1996 (available from MAFF library, Nobel House, 17 Smith Square, SW1P 3JR).

Shah R R. Thalidomide, drug safety and early drug regulation in the UK. In: *Adverse Drug React Toxicol Rev* 2001, **20** (4): 199–255. Oxford University Press.

Sweis D and Wong I C K. A survey on factors that could affect adverse drug reaction reporting according to hospital pharmacists in great Britain. *Drug Safety* 2000 **23**: 165–172.

Waller P C, Coulson R A and Wood S M. Regulatory pharmacovigilance in the United Kingdom: current principles and practice. *Pharmacoepidemiology and Drug Safety* 1996, **5**: 363–375.

Winstanley P A, Irvin L E, Smith J C, Orme M L and Breckenridge A M. Adverse drug reactions: a hospital pharmacy-based reporting scheme. *Br J Clin Pharmacol* 1989 Jul, **28** (1):113–6.

# GLOSSARY OF TERMS AND ACRONYMS

**This glossary is intended to provide a short description of the technical terms and organisations referred to in this Report. The full technical and legal definitions can be found in the relevant reference manuals and legislation.**

## **ACBS, Advisory Committee on Borderline Substances**

The Committee established in 1971 to advise Ministers of substances which may, or may not be regarded as medicines as defined in the Medicines Act.

## **ADR, Adverse Drug Reaction**

A reaction which is harmful and unintended and which occurs at a dose normally used for prophylaxis, diagnosis or treatment.

## **ADROIT, Adverse Drug Reactions On-line Information Tracking**

The MHRA's computer system for storage and analysis of ADR data.

## **AEGIS, ADROIT Electronically Generated Information Service**

A service providing subscribing organisations with access to ADR data from the ADROIT database.

## **Black Triangle ▼ Drug**

The inverted black triangle ▼ appears in the BNF, MIMS, ABPI Compendium of Data Sheets, SPC and advertising material to indicate that the medicine contains a new active substance, or a new combination of active substances, or is administered through a new route or drug delivery system or has a significant new indication which may alter the established risk/benefit profile of that drug. Black triangle ▼ drugs are monitored closely for a minimum of two years.

## **BNF, British National Formulary**

A list of medicines and monographs on their use compiled by the British Medical Association (BMA) and the Royal Pharmaceutical Society of Great Britain (RPSGB).

## **BPSU, British Paediatric Surveillance Unit**

A unit run under the auspices of the Royal College of Paediatrics and Child Health (RCPCH) to document and monitor rare and unusual conditions affecting children.

**CSD, Committee on Safety of Drugs**

The Committee on Safety of Drugs, comprising a group of independent experts in the fields of medicine, pharmacy, toxicology, pharmacology and statistics, was established in June 1963. The CSD was replaced by the Committee on Safety of Medicines (CSM) in June 1970.

**CSM, Committee on Safety of Medicines**

The CSM is one of the independent advisory committees established under the Medicines Act (Section 4) to advise the UK Licensing Authority (LA) on the quality, efficacy and safety of medicines. The CSM first met on 25 June 1970 and replaced the Committee on Safety of Drugs (CSD).

**Clinical trial**

A clinical trial is an investigation by a doctor or dentist involving administration of a medicinal product to a patient to assess the product's safety and efficacy.

**CTC, Clinical trial certificate**

An application for a clinical trial certificate (CTC) may be requested from a pharmaceutical company by the MHRA when special clinical risks are envisaged in a clinical trial and a clinical trial exemption (CTX), see below, is not considered sufficient. (During the first ten years of the control of medicines in the UK, all new active substances were evaluated in patients under a CTC.)

**CTX, Clinical trial exemption**

Since 1981, most clinical trials have been conducted under a clinical trial exemption (CTX) scheme. This exemption scheme was introduced to speed up the clinical trials of new substances.

**Controlled drugs**

The list of drugs in the Misuse of Drugs Act 1971 and Misuse of Drugs Regulations 1985, prohibit the importation, production, supply, possession with intent to supply, and possession of drugs of misuse, 'controlled drugs'. Certain controlled drugs are subject to exceptions that take account of the need for registered practitioners to use these for the medical treatment of patients.

**Current Problems in Pharmacovigilance**

*Current Problems in Pharmacovigilance* is the drug safety bulletin sent to all doctors, dentists, pharmacists and coroners in the United Kingdom by MHRA and CSM.

**EMA, the European Agency for the Evaluation of Medicinal Products**

The EMA was established in 1993, to co-ordinate and support the EC licensing system. Its main task is to co-ordinate the scientific evaluation of the safety, quality and efficacy of medicinal products for human and veterinary use throughout the European Union.

**EudraVigilance**

EudraVigilance is the European network for the exchange, processing and evaluation of Individual Case Safety Reports (ICSRs) on medicinal products authorised in the European Economic Area (EEA).

**FDA, Food and Drug Administration**

The FDA is responsible in the United States for the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, food, cosmetics, and products that emit radiation.

**FOI, Freedom of Information**

FOI legislation gives citizens a statutory right to ask for and receive information held by public bodies, unless that information is exempt from disclosure under the Act.

**GPRD, General Practice Research Database**

The GPRD is the world's largest computerised database of anonymised longitudinal patient records from general practice, containing 35 million patient years of data.

**GSL, General Sale List**

The category of licensed medicines which may be sold in places such as supermarkets and shops provided the premises can be locked and the medicines are pre-packed.

**Herbal Medicines Directive**

Two alternative systems regulate herbal medicines. (1) Licensed herbal medicines which meet safety, quality and efficacy criteria receive a marketing authorisation (MA) similar to any other licensed medicines. (2) Other herbal remedies, currently exempt from licensing requirements, meet conditions set out in Section 12 of the Medicines Act 1968. An EC Directive on traditional herbal medicinal products adopted on 11 March 2004 will, in the second half of 2005, require a simplified registration scheme for manufactured over-the-counter traditional herbal remedies.

**HIV Adverse Drug Reactions Reporting Scheme**

This Scheme is an extension of the Yellow Card Scheme, specifically to increase knowledge about the safety of medicines used in the treatment of people with HIV and to improve the safety of these medicines. The Scheme is run in collaboration between the MHRA, the Medical Research Council Clinical Trials Unit and the CSM.

**HIV ADR Reporting Scheme News**

HIV ADR Reporting Scheme News is the drug safety bulletin of the HIV Adverse Drug Reactions Reporting Scheme.

**ICH, International Conference on Harmonisation**

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) brings together the regulatory authorities of Europe, Japan, the United States and the worldwide pharmaceutical industry to achieve greater harmonisation for product registration and to reduce the need for duplicate testing during the development of new medicines.

**Independent Prescribing**

Independent Prescribing means that the prescriber takes full responsibility for prescribing a medicine to a patient and for the appropriateness of any prescription.

**Licensing Authority**

The Ministers of Health and Agriculture, with responsibilities for medicines regulation as defined in the Medicines Act.

**MA, Marketing Authorisation**

In European law medicines which meet appropriate standards of safety, quality and efficacy, are granted a Marketing Authorisation (MA), which is normally necessary before they can be sold or advertised. Previously a product licence (PL) was the accepted UK term.

**MC, Medicines Commission**

The Medicines Commission is a Section 4 Committee established in 1968. The Committee's functions were assigned under the Medicines Act 1968. Among other responsibilities, when the CSM advises refusal or revocation of a licence, there is a statutory right of appeal to the Medicines Commission.

**MCA, Medicines Control Agency**

The MCA was established in April 1989, became an Executive Agency of the DoH in July 1991 and on 1 April 1993 transferred to Trading Fund status. The MCA's primary objective, on behalf of the UK Licensing Authority (LA) was to safeguard public health by ensuring that all medicines on the UK market met appropriate standards of safety, quality and efficacy. In April 2003, the MCA merged with the Medical Devices Agency (MDA) to form the MHRA.

**MDA, Medical Devices Agency**

The MDA, an Executive Agency of the Department of Health (DoH) since 1994, merged with MCA in April 2003 to form the MHRA. The MDA, by applying standards of safety, quality and efficacy, had safeguarded the interests of patients and users of medical devices and equipment.

**MedDRA, Medical Dictionary for Regulatory Activities**

The internationally accepted medical terminology for use in drug regulation, developed under ICH and based on MEDDRA (Medical Dictionary for Drug Regulatory Affairs) which was in turn based on the MHRA's medical dictionary.

**Medicines Act**

The Medicines Act, 1968, defines the system for the licensing, manufacture, sale, supply and importation of medicinal products into the UK. It became operative on 1 September 1971. The Medicines Act brought together previous legislation on medicines and introduced new provisions for the control of medicines.

**MHRA, Medicines and Healthcare products Regulatory Agency**

The MHRA is an Executive Agency of the Department of Health with Trading Fund status. On 1 April 2003, MHRA replaced the Medical Devices Agency (MDA) and the Medicines Control Agency (MCA). The MHRA is responsible for ensuring that medicines, healthcare products and medical equipment meet appropriate standards of safety, quality, performance and effectiveness.

**NHS Direct**

The NHS telephone health enquiry service, set up in 1999, that enables patients to seek advice about minor ailments and conditions as an alternative to consulting their GP or attending an Accident and Emergency department.

**Off label use**

Use of a medicine for a disease or condition outside the terms of marketing authorisation (MA) approved by regulatory authorities.

**Orphan Drug**

A drug for a rare disease. Such products are required so rarely that an applicant for a marketing authorisation cannot be expected to provide comprehensive evidence.

**OTC, Over-the-counter products**

Over-the-counter products encompass both pharmacy (P) and General Sales List (GSL) status in the UK.

**P, Pharmacy medicine**

P medicines do not require a prescription but can only be sold or supplied at a registered pharmacy by, or under the supervision of, a pharmacist.

**P to GSL**

The legal status of a medicine can be moved from P to GSL when the Licensing Authority is satisfied that it 'can with reasonable safety be sold or supplied otherwise than by or under the supervision of a pharmacist' (Medicines Act 1968, section 51).

**PGD, Patient Group Direction**

A Patient Group Direction is defined as a written instruction for the supply or administration of medicines to groups of patients who may not be individually identified before presentation for treatment.

**Pharmacovigilance**

Pharmacovigilance is the process of (a) monitoring medicines to identify previously unrecognised, or changes in the patterns of, adverse effects; (b) assessing the risks and benefits of medicines to determine what action is necessary to improve their safe use; (c) providing information to users to optimise the safe and effective use of medicines; (d) monitoring the impact of any action taken.

**Phocomelia**

A congenital malformation (birth defect) in which the hands and feet are attached to abbreviated arms and legs like a seal's flippers. This condition was seen as a consequence of exposure of the developing foetus to thalidomide.

**PIL, Patient Information Leaflet**

A leaflet intended for the patient, supplied by the manufacturer of a licensed medicine and authorised by the MHRA. The PIL reflects the SPC for health professionals.

**PL, Product Licence**

A PL was the statutory authorisation needed to market a medicine in the UK. The term has been replaced by Marketing Authorisation (MA).

**POM, Prescription Only Medicine**

POM medicines can only be supplied in accordance with an appropriate practitioner's prescription and sold or supplied at registered pharmacy premises by, or under the supervision of, a pharmacist. An 'appropriate practitioner' is a doctor, dentist or, in certain circumstances, an independent nurse prescriber or a supplementary prescriber.

**POM to P**

This refers to the change in legal status of a Prescription Only Medicine (POM) to a Pharmacy (P) Medicine, also known as 'switching'. Before a medicine can be transferred from POM to P, the Licensing Authority must be satisfied that it will be safe to allow the medicine to be supplied without a prescription, as defined in Section 58A of the Medicines Act.

**RAMA, Remote Access for Marketing Authorisations**

An electronic service providing subscribing organisations with direct access to real-time information from MHRA on their own products, and non-confidential information on all other products authorised in the UK.



**SCOP, Sub-Committee on Pharmacovigilance**

A sub-committee of the Committee on Safety of Medicines (CSM) with the remit to advise CSM on the safety and risk/benefit of marketed medicines.

**Side effect**

A consequence other than the one for which an agent or measure is intended.

**Signal detection**

The Yellow Card Scheme is designed to detect a 'signal' that requires further pharmacovigilance investigation. A signal can be defined as an indicator or reported information that suggests a possible causal link between an adverse event and a medicine, when the postulated link was previously unknown or poorly documented.

**SPC, Summary of Product Characteristics**

Summary of Product Characteristics refers to the product information or guidance notes of a medicine for health professionals.

**Supplementary prescribing**

Supplementary prescribing is defined as a voluntary partnership between an independent prescriber (a doctor or dentist) and a supplementary prescriber, to implement an agreed patient-specific Clinical Management Plan with the patient's agreement.

**Trading Fund**

A financial framework for Government agencies, such as the MHRA, that gives the agency greater freedom to manage its financial operations.

**UK Licensing Authority**

UK Government Ministers of Health and Agriculture, with responsibilities for medicines regulation as defined in the Medicines Act.

**Working Party on Adverse Reactions**

The Working Party on Adverse Reactions, established in 1983, reviewed the Yellow Card Scheme under the chairmanship of Professor D G Grahame Smith. Their terms of reference were 'to consider how best the Committee on Safety of Medicines should fulfil its statutory functions of promoting the collection and investigation of information relating to adverse reactions, for the purpose of enabling it to give advice on safety, quality or efficacy of medicinal products; and to make recommendations.' (Annex J).

ABPI	Association of the British Pharmaceutical Industry
ACBS	Advisory Committee on Borderline Substances
ADROIT	Adverse Drug Reactions On-line Information Tracking
ADR	Adverse drug reaction
AEGIS	ADROIT Electronically Generated Information Service
ANP	Association for Nurse Prescribing
ARC	Arthritis Research Campaign
ARNS	Association of Respiratory Nurse Specialists
BHF	British Heart Foundation
BMA	British Medical Association
BMJ	British Medical Journal
BNF	British National Formulary
BPSU	British Paediatric Surveillance Unit
CHAI	Commission for Healthcare Audit and Inspection
CIOMS	Council for International Organizations of Medical Sciences
CME	Continuing Medical Education
COREC	Central Office for Research Ethics Committees
CPD	Continuing professional development
CSD	Committee on Safety of Drugs
CSM	Committee on Safety of Medicines
CTC	Clinical trial certificate
CTX	Clinical trial exemption
DNA	Deoxyribonucleic acid
DSRU	Drug Safety Research Unit
EEA	European Economic Area
EMA	European Agency for the Evaluation of Medicinal Products
EU	European Union
FDA	Food and Drug Administration
FOI	Freedom of Information
GafREC	Government arrangements for NHS Research Ethics Committees
GMC	General Medical Council
GP	General Practitioner
GPRD	General Practice Research Database
GSL	General Sales List
HIV	Human Immunodeficiency Virus
HLA	Human leukocyte antigen
HPA	Health Protection Agency

ICH	International Conference on Harmonisation
ICRS	Integrated Care Record Service
ICSR	Individual Case Safety Report
IT	Information technology
JCVI	Joint Committee on Vaccination and Immunisation
LMCA	Long Term Medical Conditions Alliance
LREC	Local Research Ethics Committee
Local REC	Local Research Ethics Committee
LSHTM	London School of Hygiene and Tropical Medicine
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
Main REC	Main Research Ethics Committee
MC	Medicines Commission
MCA	Medicines Control Agency
MCTA	Model Clinical Trial Agreement
MDA	Medical Devices Agency
MEDDRA	Medical Dictionary for Drug Regulatory Affairs
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical Research Council
MREC	Multi-centre Research Ethics Committee
NICE	National Institute for Clinical Excellence
NHS	National Health Service
NPSA	National Patient Safety Agency
NPEF	Nurse Prescribers' Extended Formulary
OTC	Over-the-counter
P	Pharmacy
PCT	Primary Care Trust
PEM	Prescription Event Monitoring
PGD	Patient Group Direction
PIAG	Patient Information Advisory Group
PIL	Patient Information Leaflet
POM	Prescription Only Medicine
PRMC	Paediatric Regional Monitoring Centre
RAMA	Remote Access for Marketing Authorisation
RCGP	Royal College of General Practitioners
RCN	Royal College of Nursing

REC	Research Ethics Committee
RMC	Regional Monitoring Centre
RPSGB	Royal Pharmaceutical Society of Great Britain
SCOP	Sub-Committee on Pharmacovigilance
SEAG	Scientific and Ethical Advisory Group
SHSCG	Safety in Health and Social Care Group
SPC	Summary of Product Characteristics
The Act	The Data Protection Act
<i>The Code</i>	<i>The Code of Practice on Access to Government Information</i>
VAERS	Vaccine Adverse Events Reporting Scheme
WHO	World Health Organization

# ANNEXES

## **Annexes within the Report**

Annex A: Yellow Card

Annex B: Steering Committee membership

Annex C: Sir Derrick Dunlop letter of 1964 to all UK doctors

Annex D: Press release – announcement by Lord Warner

Annex E: Consultation letter (minus annexes)

Annex F: List of key stakeholder meetings

Annex G: ADR reports received by year via the Yellow Card Scheme since 1964

## **Annexes on the MHRA website**

<http://medicines.mhra.gov.uk/ourwork/monitorsafeequalmed/yellowcard/accessreviewreport.htm>

Annex H: Annexes of Consultation letter

Annex I: Consultation responses

Annex J: Report of the Working Party on Adverse Reactions. June 1983

Annex K: Report of the Working Party on Adverse Reactions. July 1985

Annex L: Minutes of meetings of the Steering Committee

**ANNEX A**  
YELLOW CARD



## SUSPECTED ADVERSE DRUG REACTIONS

If you are suspicious that an adverse reaction may be related to a drug or combination of drugs please complete this Yellow Card. For reporting advice please see over. Do not be put off reporting because some details are not known.

<b>PATIENT DETAILS</b>		Patient Initials: _____	Sex: M / F	Weight if known (kg): _____
Age (at time of reaction): _____		Identification number (Your Practice / Hospital Ref.): _____		
<b>SUSPECTED DRUG(S)</b>				
Give brand name of drug and batch number if known				
_____	Route	Dosage	Date started	Date stopped
_____	_____	_____	_____	_____
Prescribed for _____				
<b>SUSPECTED REACTION(S)</b>				
Please describe the reaction(s) and any treatment given:				
				<b>Outcome</b>
				Recovered <input type="checkbox"/>
				Recovering <input type="checkbox"/>
				Continuing <input type="checkbox"/>
				Other <input type="checkbox"/>
Date reaction(s) started: _____		Date reaction(s) stopped: _____		
Do you consider the reaction to be serious? Yes / No				
If yes, please indicate why the reaction is considered to be serious (please tick all that apply):				
Patient died due to reaction	<input type="checkbox"/>	Involved or prolonged inpatient hospitalisation	<input type="checkbox"/>	
Life threatening	<input type="checkbox"/>	Involved persistent or significant disability or incapacity	<input type="checkbox"/>	
Congenital abnormality	<input type="checkbox"/>	Medically significant; please give details: _____		
<b>OTHER DRUGS (including self-medication &amp; herbal remedies)</b>				
Did the patient take any other drugs in the last 3 months prior to the reaction? Yes / No				
If yes, please give the following information if known:				
Drug (Brand, if known)	Route	Dosage	Date started	Date stopped
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
<b>Additional relevant information</b> e.g. medical history, test results, known allergies, rechallenge (if performed), suspected drug interactions. For congenital abnormalities please state all other drugs taken during pregnancy and the last menstrual period.				
<b>REPORTER DETAILS</b>			<b>CLINICIAN (if not the reporter)</b>	
Name and Professional Address: _____			Name and Professional Address: _____	
_____			_____	
Post code: _____			Post code: _____	
Tel No: _____			Tel No: _____	
Speciality: _____			Speciality: _____	
Signature: _____			Date: _____	
				If you would like information about other adverse reactions associated with the suspected drug, please tick this box <input type="checkbox"/>

\* This is to enable you to identify the patient in any future correspondence concerning this report

Please attach additional pages if necessary

## **ANNEX B**

### **STEERING COMMITTEE MEMBERSHIP**

**Dr Jeremy Metters CB (Chairman)**

Her Majesty's Inspector of Anatomy.

Former Deputy Chief Medical Officer, Department of Health (1989–1999).

**Professor Christine Bond BPharm (Hons), FRPharmS, PhD, MEd, MFPH (Hon)**

Professor of Primary Care: Pharmacy, Department of General Practice and Primary Care, University of Aberdeen. Part time Consultant in Pharmaceutical Public Health, NHS Grampian. Member of the National Pharmaceutical Forum (Scotland), the CSO Health Services Research Committee, and the MREC for Scotland.

**Professor Gordon Duff BA MA BM BCh PhD FRCP FRCPE FMedSci**

Director, Division of Genomic Medicine, University of Sheffield. Honorary Consultant, Sheffield Teaching Hospitals NHS Trust. Chairman, Committee on Safety of Medicines (CSM).

**Ms Kristin McCarthy MA BA**

Director of the Developing Patient Partnerships (DPP) (formerly Doctor Patient Partnership). She holds an MA in Medical Law and Ethics and a BA in Political Science. Director of DPP's trading company, DPP2000. Trustee of the Men's Health Forum and on the Executive Group of Ask About Medicines Week.

**Dr Jane Richards OBE**

Retired General Practitioner. Previous Chairman of Prescribing Sub-Committee of BMA GP's Committee and member of Joint Formulary Board of the British National Formulary (BNF).

**Dr Sandy Thomas**

Director of Nuffield Council on Bioethics which was established by the Trustees of the Nuffield Foundation in 1991 to identify, examine and report on ethical questions raised by recent advances in biological and medical research.



**Dr Simon Thomas MBBS MRCP MD FRCP**

Consultant physician, Newcastle Hospitals NHS Trust. Reader in Therapeutics, University of Newcastle Upon Tyne. Chairman of Northern & Yorkshire MREC. Head of CSM Northern & Yorkshire Regional Monitoring Centre (RMC). Member of CSM's Sub-Committee on Pharmacovigilance (SCOP).

**Mr Philip Webb**

Member of the Human Genetics Commission since 2000 and Chair of its Genetic Services Sub-Group. On the Board of Trustees of the Genetic Interest Group and sits on the police National DNA Database Board.

**Mr Simon Williams\***

Director of Policy, the Patients Association.

---

\* Mr Simon Williams was only available to attend the 2nd Steering Committee meeting held in December 2003

## ANNEX C

### SIR DERRICK DUNLOP LETTER OF 1964 TO ALL UK DOCTORS

#### COMMITTEE ON SAFETY OF DRUGS

Queen Anne's Mansions, Queen Anne's Gate

LONDON S.W.1

Telephone: TRAFALGAR 6121

4 May 1964

Dear Doctor,

As Chairman of the Committee on Safety of Drugs I am writing to every member of the medical profession in the United Kingdom to ask for help. We ask you to report to us promptly details of any untoward condition in a patient which *might* be the result of drug treatment. We will also from time to time seek your co-operation in our research into adverse reactions by asking you to give us information concerning the health of patients who are receiving or have received drugs about which suspicions of serious side effects have been aroused.

#### REPORTING ADVERSE REACTIONS: THE EARLY WARNING SYSTEM

The Committee is establishing a Register of Adverse Reactions to Drugs. If adverse reactions are promptly and accurately reported to us it will be possible for us to issue warning to doctors if we find that the frequency or seriousness of reactions to any particular drug constitutes a hazard to patients. Special business reply post-cards have been printed for these reports and a supply is enclosed.

This early warning system depends for its success on the reports from doctors and for this reason the form has been kept brief so that you can complete it without delay. We ask you to give us the name of the patient concerned so that we can link up reports which may come to us both from the family doctor and a hospital doctor about a reaction experienced by the same patient. It will sometimes be necessary for our Medical Assessor to ask you for further information and if he does he will send a business reply addressed envelope for your reply.

#### FURTHER RESEARCH INTO ADVERSE REACTIONS

In order to estimate the seriousness of reported adverse reactions it will be necessary for the Committee to find out how frequently reactions are occurring in relation to the number of times the drug is prescribed. The reports of adverse reactions sent to the Sub-Committee in accordance with the early warning system cannot give us this information with any degree of accuracy since to a doctor looking at cases in isolation it may not be obvious that an effect has an association with a drug. We can only determine the real ratio of adverse reactions to prescriptions by asking a number of doctors who have prescribed the drug about their experience in its use. We intend to take a sample of prescriptions written both by family doctors and by hospital doctors throughout the United Kingdom and then write to each doctor concerned asking him if he has noticed any particular untoward effects during or after treatment of the patients. Brief forms for reply and prepaid addressed envelopes will be sent with any enquiries which we hope will not be frequent.

#### THE SPECIAL CONTRIBUTION OF GENERAL PRACTITIONERS IN NORTHERN IRELAND

I wish particularly to ask for the help of general practitioners in Northern Ireland. This is at present the only place in the United Kingdom, and probably in the world, where it is possible to find out accurately for a known population, the incidence of side effects when a drug has been prescribed in general practice. This is because the Northern Ireland General Health Services Board has for many years used mechanical methods of coding and tabulating details of prescriptions, which have as yet no counterpart elsewhere. The Committee on Safety of Drugs has been offered co-operation by the Northern Ireland Ministry of Health and Local Government and the General Health Services Board in the use of this machinery for its work. It will be possible to trace rapidly

all prescriptions issued by general practitioners in Northern Ireland for a given drug and then to write to the doctors concerned to ask whether patients have or have not had any ill effects that might have been due to the drug. The information obtained in this new and important form of general practitioner research will be of particular value to the Committee.

#### CONFIDENTIAL NATURE OF ALL INFORMATION

All the reports or replies that the Committee receive from doctors will be treated with complete professional confidence by the Committee and their staff. The Health Ministers have given an undertaking that the information supplied will never be used for disciplinary purposes or for enquiries about prescribing costs.

#### THE IMPORTANCE OF THESE REPORTS

We appreciate that the reporting of adverse reactions and replying to our enquiries is an added burden for members of our profession and we shall restrict our enquiries to the minimum necessary for ensuring the safety of drugs. We are confident that you will give us your co-operation in this matter, for this is the only way by which knowledge of the presence and prevalence of adverse reactions to drugs can be obtained. Sometimes it may become clear that a drug should only be used with great caution, but equally important, we may be able to obtain evidence that anxieties about a useful drug are unfounded. Only with the help of all doctors will it be possible for us to keep the profession promptly and accurately informed about such matters which are of great consequence to the health of patients.

Yours sincerely,

A handwritten signature in cursive script, reading "Derrick Deutscher". The signature is written in black ink and includes a long horizontal flourish at the bottom.

## **ANNEX D**

### **PRESS RELEASE – ANNOUNCEMENT BY LORD WARNER**

Monday 21st July 2003

HEALTH MINISTER WELCOMES REVIEW OF ACCESS TO MEDICINES SAFETY DATA

An independent review of the Medicines and Healthcare products Regulatory Agency's (MHRA) drug side effect reporting system – the Yellow Card Scheme – was welcomed today by Health Minister, Lord Warner.

The review is in response to an increase in requests for access to yellow card data which raise major issues in relation to public health. Looking at the access to and use of collected data, the review will be led by Dr Jeremy Metters CB, the former Deputy Chief Medical Officer. Acting as an early warning system to identify drug safety issues, the UK's Yellow Card scheme is recognised as one of the best spontaneous reporting schemes in the world. The introduction of the online electronic yellow card in October modernised the way in which healthcare professionals submit suspected reactions. This, together with the inclusion of nurse reporting, and patients reporting via NHS Direct have delivered further improvements.

**Lord Warner said:**

'After almost 40 successful years, our aim is to maintain the capacity of the scheme to deliver public health benefits and prevent potential abuse of this important data in the future. It is essential to determine in what form this important data should be made available. Given the complexities and sensitivities of the issues, and the range of stakeholders involved, the outcome will be published and publicly consulted upon.'

**Chairman of the MHRA, Professor Alasdair Breckenridge said:**

'The Yellow Card Scheme has been the cornerstone of monitoring drug safety for nearly 40 years and has an excellent track record in protecting public health. The data generated by this scheme is very important and it is right that we take a careful and important look at how we safeguard its use in the future.'

**Dr Metters said:**

'I am honoured to be heading up this review of such a hugely complex area. There are issues around the confidence of health professionals in the confidentiality of the scheme, and how the data could be used to unlock the potential for so called "designer medicines". Ethical and financial questions are also raised as to the use of an important public health tool for commercial gain.'

**Notes to Editors:**

1. The terms of reference for the review are:

To identify and describe the range of issues which should be considered when considering access to data generated by the Yellow Card scheme including

- ethical
- operational
- financial and
- statutory (including open Government/FOI).

To identify relevant stakeholders to the scheme and to define how such interests arise.

To consider in what circumstances access to the data generated by the scheme could be said to be in the public interest and the extent to which this falls within existing legal provisions.

To make proposals for guiding principles and a mechanism for handling such requests.

To make recommendations for action.

The Review should report to the Chairman of the MHRA by the end of 2003.

2. The Yellow Card Scheme was set up in 1964 following the Thalidomide tragedy to provide a system for early detection of emerging drug safety hazards and the routine monitoring for all medicines in clinical use. Suspected adverse reactions to marketed medicinal products are reported to the Committee on Safety of Medicines (CSM)/MHRA, which are jointly responsible for running the scheme. Reports are primarily submitted voluntarily by GPs, hospital doctors, dentists, coroners, pharmacists and nurses. Reports are also received via the pharmaceutical industry, which has a statutory obligation to report suspected serious ADRs.
3. The CSM is an independent Committee of experts that advise Government on the safety, quality and effectiveness of medicines, including vaccines. It is also responsible for encouraging the collection and investigation of reports on suspected adverse reactions to medicines already on the market. The MHRA is the executive arm of the UK's Drug Licensing Authority and is responsible for all aspects of the regulation of medicines in the UK.
4. Dr Jeremy Metters trained in hospital medicine, becoming a fellow of the Royal College of Obstetricians and Gynaecologist. He was Deputy Chief Medical Officer at the Department of Health from 1989 to 1999 and since then has been Her Majesty's Inspector of Anatomy. Dr Metters was previously Chair of the Council of Europe Ad Hoc Committee on Bioethics.
5. For media enquiries only, please contact Steve Ryan or Alison Langley in the Department of Health Media Centre on 020 7210 5226/5649.

## **ANNEX E**

### **CONSULTATION LETTER (MINUS ANNEXES)**

**Review of Access to Yellow Card Data**  
**Room 14–111**  
**Market Towers**  
**1 Nine Elms Lane**  
**London SW8 5NQ**

INDEPENDENT REVIEW OF ACCESS TO YELLOW CARD DATA: LETTER TO STAKEHOLDERS

6 October 2003

Dear Sir/madam

Independent Review of Access to Yellow Card Data

This letter is addressed to all the organisations and individuals who have an interest in the collection and analysis of data on suspected adverse drug reactions (Yellow Card data). The Terms of Reference for the Review are attached at A and were announced by Lord Warner on 21st July. We would welcome all views.

Since 1964, the "Yellow Card Scheme" has been collecting information on suspected adverse drug reactions to medicines in the UK from health professionals (see Annex B). The Scheme is the cornerstone of medicines safety monitoring and has been used by the Medicines and Healthcare products Regulatory Agency (MHRA) and its predecessors, and its expert advisory body, the Committee on Safety of Medicines, as a key tool to protect public health. The Scheme provides a system for both the early detection of emerging drug safety hazards and the routine monitoring of all medicines in clinical use.

It is vital that any change in access to the Yellow Card data should not damage the Scheme's ability to protect public health by discouraging reporters on whose continued support the Scheme is entirely dependent.

A short account of the Yellow Card Scheme is attached at C to provide background.

The primary purpose of the Review of Access to Yellow Card data is to consider whether, and if so under what conditions and for what purposes, the data should be made more widely available. It has been stimulated in part by increasing numbers of requests by independent researchers in academia and clinical institutions, who wish to use the data for research and audit purposes and in part by the potential for new uses, eg in researching the use of genetics to reduce the burden of adverse drug reactions. Other aspects of the Scheme will be considered during the Review.

Each event reported through the Yellow Card Scheme relates to what happened to an individual patient, who may or may not know that his/her experience has been reported. Although the Yellow Cards have been anonymised since 2000 (and earlier reports have been anonymised retrospectively), widening the access to these data poses questions of patient confidentiality, ethics and the law that need to be carefully considered against the potential benefits to patient safety, public health and other improvements.

The Steering Committee for the Review, whose membership is attached at D, would welcome your comments on the following issues:

**Public Health**

Should data submitted in confidence to MHRA/CSM be made more widely available for uses outside monitoring and control of medicines safety?

What are the implications for patient safety, public health and the future of the Scheme of widening access to data or changing the reporting procedures?

**Ethics**

What are the ethical issues raised in offering wider access to use of Yellow Card data?

If the data were to be used for research, how should the ethics of individual research proposals be evaluated?

**Research**

Should research be permitted with or without the agreement of the patient whose suspected adverse event has been reported?

Should research that includes genetic information or analysis be permitted?

**Controls on use of Yellow Card Data**

What safeguards are required to ensure use of the data is likely to promote public health?



Should aggregated data be made available to NHS trusts/primary care trusts for their use? If so, in what form and for what purposes?

**Conditions on access**

If these data are to be more widely available to researchers external to the MHRA, what conditions of access [ethical/financial/potential impact on public health] should be applied?

Should data from the Yellow Card Scheme be made available for direct or indirect financial gain?

**Legal issues**

Does the existing legal framework sufficiently protect data subjects and reporters or in any way inhibit the reporting of adverse drug reactions?

If so what changes are required for improvement?

**Operational impact**

As the Government has a statutory responsibility to have such a scheme in place, how should financial consequences of wider access to data be addressed?

What are the operational implications of wider access eg for the maintenance of the database and its continued utility for drug safety monitoring?

What implications might changes to the use of the data have on reporting to the scheme?

**Strengthening of the Yellow Card Scheme**

How might the reporting Scheme better promote and protect public health if changes are made to access to the data?

**How might the reporting Scheme be strengthened?**

**Any other issues**

Are there any other issues we need to consider in the context of altered access to the Yellow Card data?

Please do share this letter with anyone who you feel may have an interest in this area.

Your response and those of all stakeholders interested in the issues raised by altered access to Yellow Card data will be welcomed by the Steering Committee for the Review. Responses should be sent to the above address by 9 January 2004.



To help informed debate on the issues raised by this consultation exercise, and within the terms of the Code of Practice on Access to Government Information ('Open Government'), the agency intends to make copies of comments received publicly available. Unless you state otherwise we will assume that you have no objections to your comments being publicly available.

Yours faithfully,

Dr Jeremy Metters CB

On behalf of the Steering Committee for the Review of Access to Yellow Card Data

## ANNEX F

### LIST OF KEY STAKEHOLDER MEETINGS

<b>Key stakeholder meetings</b>			
	<i>Date</i>	<i>Key Stakeholders</i>	
1	4th November 2003	Dr Andrew Herxheimer Mr Charles Medawar	Independent researchers
2	4th November 2003	Dr John Boyce	Commission for Healthcare Audit and Inspection (CHAI)
3	11th November 2003	Professor Parveen Kumar	Medicines Commission
4	19th November 2003	Professor Stephen Evans	London School of Hygiene and Tropical Medicine
		Professor Saad Shakir	Drug Safety Research Unit
5	19th November 2003	Ms Jackie Glatter Ms Wendy Garlick	Consumers' Association
6	26th November 2003	Professor Stephen Jackson	Royal College of Physicians
		Dr Ross Taylor	Royal College of General Practitioners (RCGP)
7	9th December 2003	Mr Clive Flashman Professor David Cousins	National Patient Safety Agency (NPSA)
		Professor David Barnett Dr Seren Philips	National Institute for Clinical Excellence (NICE)
8	10th December 2003	Ms Maureen Williams	Nursing and Midwifery Council (NMC)
		Dr Molly Courtenay	Royal College of Nursing (RCN)
		Dr George Rylance	Royal College of Paediatrics and Child Health (RCPCH)
9	11th December 2003	Professor Martin Kendall	CSM Sub-Committee on Pharmacovigilance (SCOP)
10	11th December 2003	Dr Richard Tiner Mrs Nicky Lilliott	Association of the British Pharmaceutical Industry (ABPI)
11	19th December 2003	Professor Terry Stacey	Central Office for Research Ethics Committees (COREC)
12	19th January 2004	Ms Pamela Warrington	Deputy Chief Pharmacist, Scottish Executive
13	19th January 2004	Mr Rob Darracott	Royal Pharmaceutical Society of Great Britain (RPSGB)

	<i>Date</i>	<i>Key Stakeholders</i>	
14	20th January 2004	Dr Peter Fellows	General Practitioners Committee (GPC)
15	23rd January 2004	Dr Andrew Freeman Dr Will Maier Dr Andrew Rut	GlaxoSmithKline (GSK)
16	23rd January 2004	Mr Paul Robinson	Prescribing and Prescribing Projects, Department of Health (DoH)
		Mr Martin Bagwell	Executive Support, Medicines and Healthcare products Regulatory Agency (MHRA)
17	29th January 2004	Dr Norman Morrow Dr Dennis Morrison Dr Sean O'Hare Mr Brian Godfrey Dr Glenda Mock Ms Liz Qua Ms Jane Graham Ms Lisa Smith Dr Carmel Hughes Ms Nikki Patterson Mr David Reilly Mr Geoff Dudgeon Mr Kieran Gilmore Dr Maura Briscoe	Safety in Health and Social Care Group (SHSCG), Department of Health Social Services and Public Safety, Northern Ireland
18	3rd February 2004	Ms Jane O'Brien Ms Susan Doohan	General Medical Council (GMC)
19	9th February 2004	Ms Melinda Letts	Long Term Medical Conditions Alliance (LMCA)
20	11th February 2004	Professor Elizabeth Miller Dr Nick Andrews Dr Helen Campbell	Health Protection Agency (HPA)
21	11th February 2004	Professor Michael Langman	Joint Committee on Vaccination and Immunisation (JCVI)
		Dr David Salisbury	Principal Medical Officer, DoH
22	24th February 2004	Professor Munir Pirmohamed Dr Nick Bateman Dr Robin Ferner Dr Simon Thomas	Regional Monitoring Centres (RMCs)
23	2nd March 2004	Ms Jenny Hope	Daily Mail
		Ms C Pedder	Pulse
		Mr C Duffin	Nursing Standard
		Ms Monica Polak	GP
		Ms Sarah Boseley	Guardian
		Ms Karen Allen	BBC 6 o'clock news
24	24th March 2004	Ms Sarah Ramsay	The Lancet
		Ms Annabelle Ferriman	British Medical Journal (BMJ)

## ANNEX G

### ADR REPORTS RECEIVED BY YEAR VIA THE YELLOW CARD SCHEME SINCE 1964

Number of UK Adverse Drug Reaction (ADR) Reports Received by Year

