Pharmacovigilance – how the MHRA monitors the safety of medicines

Before a medicine is marketed, any experience of its safety and efficacy is limited to its use in clinical trials. However, the conditions under which patients and medicines are studied in clinical trials do not necessarily reflect the way the medicines are used in hospitals or general practice once they are marketed. For example, at the time of its licensing, a medicine will only have been tested in a relatively small number of patients for a limited length of time.

Despite the extensive research in animals and clinical trials in humans for a specific medicine, some adverse drug reactions (ADRs) may not be seen until a very large number of people have received the medicine. Therefore it is vital that the safety of all medicines is monitored throughout their marketed life - this is known as **pharmacovigilance**.

Pharmacovigilance involves:

- monitoring the use of medicines in everyday practice to identify previously unrecognised adverse effects or changes in the patterns of adverse effects
- assessing the risks and benefits of medicines in order to determine what action, if any, is necessary to improve their safe use
- providing information to healthcare professionals and patients to optimise safe and effective use of medicines
- monitoring the impact of any action taken

Risks and benefits of medicines

For a medicine to be considered safe, its expected benefits should be greater than any associated risks of harmful reactions. All medicines can cause reactions; however, most people take medicines without suffering any serious side effects. Healthcare professionals should be able to discuss such information with patients, parents and carers, be vigilant in the detection of suspected ADRs and prompt in reporting them via the Yellow Card Scheme.

How do we monitor the safety of licensed medicines?

Information sources used for pharmacovigilance Information from many sources is used for pharmacovigilance. These include:

- spontaneous adverse drug reaction (ADR) reporting schemes, for example, the Yellow Card Scheme (see below)

- clinical and epidemiological studies
- worldwide published medical literature
- pharmaceutical companies
- worldwide regulatory authorities
- morbidity and mortality databases

Other information sources are used to confirm, characterise and assess the frequency of the reported adverse reactions.

Information from all of these sources is carefully screened and may identify unexpected ADRs, indicate that certain side effects occur more commonly than previously believed, or that some patients are more susceptible to some effects than others. Such findings can lead to changes in the marketing authorisation license of the medicine, such as:

- restrictions in use
- changes in the specified dose of the medicine
- introduction of specific warnings of side-effects in the product information

Information collected through the Yellow Card Scheme is an important tool in helping MHRA and CHM monitor medicine safety. Yellow Card reports of suspected ADRs are evaluated, together with additional sources of evidence such as worldwide literature, in order to detect previously unidentified hazards or side effects.

If a new side effect is identified, information is carefully considered in the context of the overall side effect profile for the medicine, and how it compares with other medicines used to treat the same condition.

Regulatory actions to minimise risk

When necessary, the MHRA may take action to ensure that a medicine is used in a way which minimises risk, and maximises benefits to the patient. Such action may include:

- changes to warnings in the product information or on the package label
- restricting the indications for use of a medicine
- changing the legal status of a medicine, for example, from over-the-counter to prescription only
- in rare circumstances, removal of the medicine from the market, if the risks of a medicine are found to outweigh the benefits

The MHRA works closely with other European regulatory authorities on pharmacovigilance matters.

Communication with healthcare professions and patients

MHRA recognise that communication with health professionals and patients both to warn about adverse effects and to provide feedback of information is an important aspect of

pharmacovigilance. We provide feedback through:

- updating patient information leaflets (PILs) and Summaries of Product Characteristics (SPCs) for medicines when new safety issues are identified
- letters are sent to all doctors and pharmacists by post or electronic cascade highlighting urgent warnings about drug hazards
- publication of safety information in our drug safety bulletin 'Drug Safety Update' – the latest advice for medicines users – our monthly bulletin Drug Safety Update contains the latest advice for safer use of medicines and is available on our website at 'Drug Safety Update' - if you are a healthcare professional and would like to receive a notification of each new bulletin, please send your email address to registration@mhradrugsafety.org.uk
- fact sheets on major safety issues, which are produced for both healthcare professionals and patients
- safety alerts are published on the MHRA website

What the MHRA does with Yellow Cards

Yellow Card reports are evaluated, alongside other information and evidence on medicine safety as described above (information sources used for pharmacovigilance) to determine whether any regulatory action is required to allow medicines to be used more safely and effectively. If the available evidence is insufficient at the time the issue would remain under close review as further data becomes available. If a new side effect is identified, information is carefully considered in the context of the overall side effect profile for the medicine, and how it compares with other medicines used to treat the same condition.

Rarely if the risks are considered to outweigh the benefits a product it may be taken off the market. More usually regulatory action can lead to restrictions in use, reclassification of the medicine, refinement of dose instructions or the introduction of specific warnings of side-effects in product information, which allow medicines to be used more safely and effectively. Any new suspicions of harmful effects are followed (when necessary) with communications, regulatory action to minimise risks and audit and maximises benefit to the patients taking the medicine.

The lifecycle of a Yellow Card

All Yellow Card reports received either on paper or electronically are promptly entered onto the MHRA's adverse drug reaction (ADR) database so that they are available for signal detection. Signal detection is the continual review of ADR reports to identify previously unrecognised concerns about medicines, vaccines or blood products, which may warrant further action. Sometimes a signal can comprise a change in the pattern or frequency of ADRs already associated with a medicine; this, too, may warrant further action.

The Yellow Card Scheme's contribution to detecting these new concerns is immensely valuable. Analysis of data from the Yellow Card Scheme, alongside information from other sources to quantify the risk, leads to a decision on how best to act to protect public health. Yellow Card Scheme procedures are specifically designed to ensure prompt availability of

Yellow Card data for signal detection.

Data entry

Paper Yellow Cards require manual data entry, whereas electronic Yellow Cards are automatically loaded into the database then reviewed to ensure data has been entered correctly. Yellow Card Scheme staff ensure that the database accurately reflects Yellow Card reports and that the process fully supports prompt and effective action on emerging information on harms. Information from Yellow Card reports is entered onto a database and checked as follows:

1. Minimum required details—such as patient details, reporter details, name of suspect drug/medicine, and reaction—are present. All Yellow Card reports are acknowledged—either by email or electronic Yellow Card or by letter and are accompanied by a copy of the submitted Yellow Card report.
2. All remaining information provided on the Yellow Card is then entered.
3. A final quality audit step is carried out to ensure accuracy of the data.

Once all the information is on the database, a number of processes start.

Signal detection

Using specialised software, Yellow Card data are subjected to statistical analysis of all drug-reaction combinations on the database. This identifies ‘signals’—drug-reaction combinations that occur more frequently than would be expected when compared to the background frequency of other drug-reaction combinations in the database.

Signals that meet defined criteria are evaluated further by a team of safety experts to assess the likelihood of causal relationship between the drugs and reported reactions.

Assessment and follow-up for further information

After entry onto the database, Yellow Card reports are assessed by a team of physicians, pharmacists and scientists, with expertise in assessing the benefits and risks of medicines. Importantly, at this stage we also use search other data sources to investigate the causal relationship between the medicines and reported reactions and to identify possible risk factors e.g. age, underlying disease and genetic predisposition. These sources include, for example, case reports in the literature, information from pharmaceutical companies, pre and post-marketing clinical trials, epidemiological studies and data from other medicine regulatory authorities and from global ADR databases.

Occasionally further information or clarification is requested from the reporter so that the report can be properly evaluated.

Regulatory action and communication

A number of options for action are available to minimise the risk from a newly confirmed adverse effect. In rare circumstances, a medicine may be withdrawn from the market if its risks are considered to outweigh its benefits. More usually, the risk of a side effect may be avoided or reduced by restricting its indications, reducing the recommended doses, changing the duration of treatment, or by adding special warnings and precautions.

The Commission on Human Medicines (CHM) and its Pharmacovigilance Expert Advisory Group (PEAG) advises the MHRA on medicine safety issues. Such issues are put to Committees which include representatives from all European Union regulatory authorities. Changes as a result of new information on harm can by communicated in the product literature (summary of product characteristics and patient information leaflet); clinicians are also alerted of important changes by means of the monthly bulletin Drug Safety Update or by direct communication, usually from the pharmaceutical company. The MHRA also strives to alert secondary information providers (such as the British National Formulary and clinical software suppliers) of new information on adverse reactions.

Data provision

Another important function is the provision of anonymised data. The MHRA supplies anonymised case details (with reporter details removed and patient details anonymised) to pharmaceutical companies so they can perform safety analyses.

We also publish cumulative listings of all suspected ADRs received. The listings are called Drug Analysis Prints (DAPs) and are available on our website. These data are also used for answering enquiries on suspected adverse reactions from healthcare professionals and members of the public.

Patients and health professionals reporting suspected adverse drug reactions to the Yellow Card Scheme help contribute to these important processes.