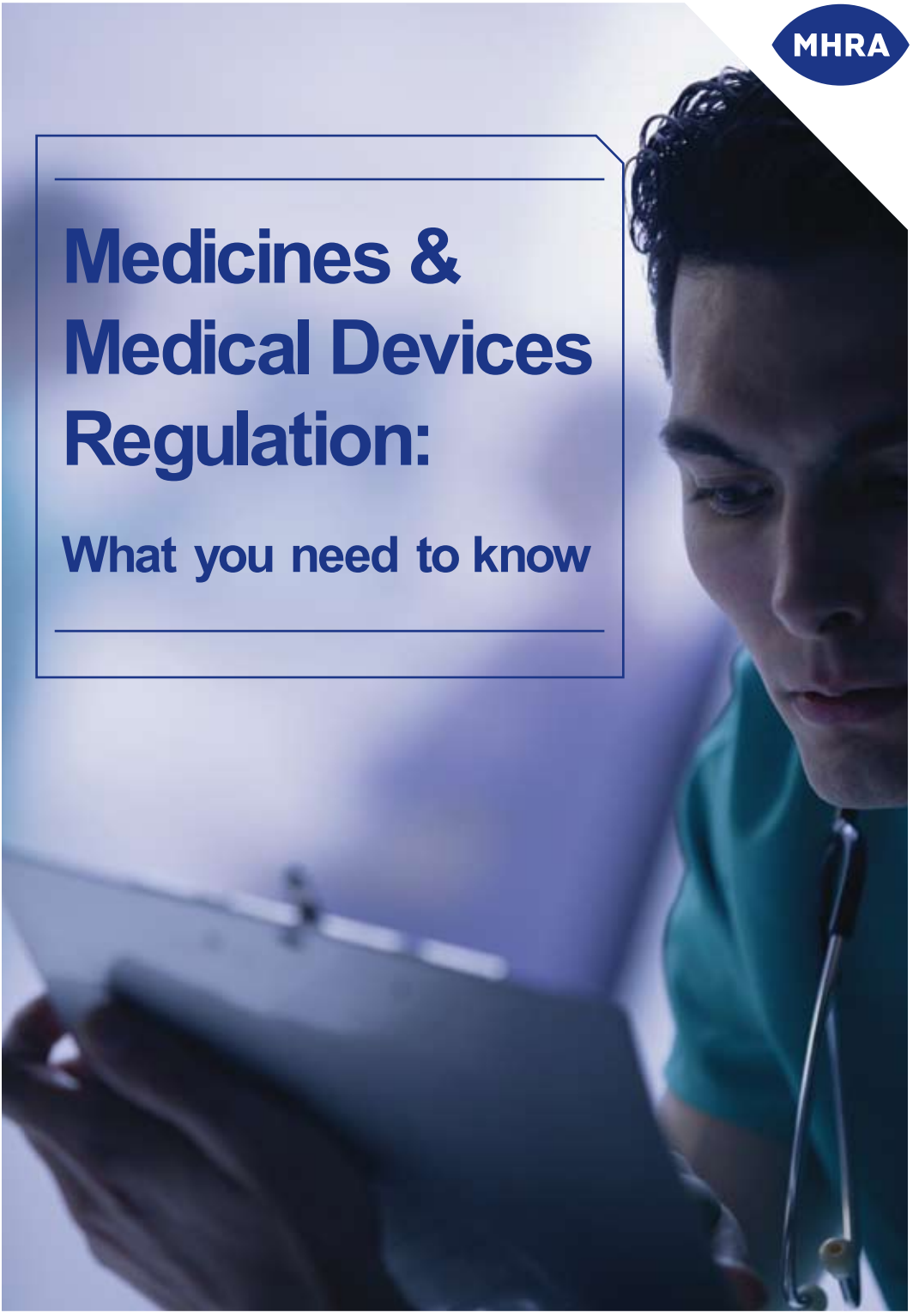

MHRA
Medicines &
Medical Devices
Regulation:
What you need to know

Safeguarding public health through the effective regulation of medicines and medical devices

Medicines & Medical Devices Regulation

What is the MHRA?

The Medicines and Healthcare products Regulatory Agency (MHRA) is a government body which was set up in 2003 to bring together the functions of the Medicines Control Agency (MCA) and the Medical Devices Agency (MDA).

These include the regulation of medicines and medical devices and equipment used in healthcare and the investigation of harmful incidents. The MHRA now also looks after blood and blood products, working with UK blood services, healthcare providers, and other relevant organisations to improve blood quality and safety. The principal aim of the Agency is to safeguard the public's health. It does this by making sure that medicines and medical devices—from painkillers to pacemakers—work properly and are acceptably safe; and by responding promptly when new concerns come to light. No product is completely free of risk but sound evidence underpins all the MHRA's decisions to ensure that these risks are minimised.

When is a product acceptably safe?

No product is 100 per cent safe, because all products have side effects. These may be very minor, but they may also be serious.

For example, cancer treatments may make the difference between living and dying. They can also make patients feel very unwell and increase the chances of infections. Aspirin reduces inflammation and fever. But it can also irritate the lining of the stomach.

Different people respond to medicines differently. Several factors can influence the chances of side effects. These include the prescribed dose, the condition being treated, the age and sex of the patient, and other treatments which the patient may be taking, including herbal/complementary medicines.

Medicines are very thoroughly trialled on thousands of people and must meet rigorous standards before they are licensed. When used more generally by a wider population, other side effects can come to light.

The key questions for the MHRA are:

- Do the advantages outweigh the dis-advantages of taking the medicine?
- Does the medicine do the most good for the least harm for most people who will be taking it?
- Are the side effects acceptable?

A high level of side effects may be acceptable for a medicine used to treat a life threatening illness, for example, but not in one used for a common minor ailment.

Ultimately, patients and their healthcare professionals have to weigh up the pros and cons of each medicine when deciding on the most appropriate treatment.

The history of UK regulation

The formal regulation of medical devices really began in the mid 1990s - a European wide initiative. Prior to that, the Scientific and Technical Branch (STB - established in the late 1960s) and the Department of Health had been set up to improve the quality and safety of medical equipment. During the 1980s, the STB became part of the NHS Procurement Directorate, which was later split into the NHS Supplies Authority and the Medical Devices Directorate (MDD). The MDD in effect became the Medical Devices Agency in 1994 which then merged with its medicines counterpart in 2003 to become the MHRA. The Committee on the Safety of Devices is an independent body of experts which advises the MHRA.

The outcry over thalidomide effectively kick-started medicines regulation in the UK. Thalidomide was prescribed during the late 1950s and early 1960s to relieve morning sickness in the first few months of pregnancy, but caused unpredicted serious birth defects.

In a bid to prevent a similar occurrence, the Committee on Safety of Drugs was set up in 1963. This subsequently became the Committee on Safety of Medicines (CSM) under the terms of the Medicines Act of 1968, which provided the legal framework for the control of medicines in the UK. In 2005 this committee became the Commission on Human Medicines (CHM).

The Act required medicines to be licensed before being allowed onto the UK market. Many of the provisions of the Act have now been superseded by regulations implementing European legislation on medicines. The Medicines Control Agency was created in 1989, and merged with the Medical Devices Agency to become the MHRA in 2003. CHM provides independant expert advice to the MHRA.

How does the MHRA work?

The Agency has the power to withdraw a product from the market, and in the case of medicines, to suspend production. The Agency can also prosecute a manufacturer or distributor if the law has been broken.

The regulations need to be robust enough to protect the public's health, and this costs money. The MHRA is funded largely by public monies from government for the regulation of devices, and by fees from the pharmaceutical industry for the regulation of medicines.

The Agency's regulatory decisions are impartial and based solely on the extensive evidence of quality, safety, and efficacy required for each product. Different products are treated differently but the MHRA considers the particular characteristics, drawbacks and advantages of each one.

Additionally, the MHRA's employees are not allowed to have any personal financial ties to pharmaceutical companies or medical device manufacturers.

The MHRA works closely with the European regulator, the European Medicines Agency (EMEA), and is recognised as a trusted and independent source of expertise throughout Europe.

The MHRA also collaborates with other international regulators, such as the US Food and Drug Administration (FDA), and UK government agencies involved in healthcare, including the National Patient Safety Agency (NPSA) and the National Institute for Health and Clinical Excellence (NICE).

The MHRA is fully accountable to both the government and the public. Details of its operations and licensing decisions are freely available on the MHRA website: www.mhra.gov.uk.

How does licensing and authorisation work?

Licences for medicines are granted only when a product meets high standards of safety and quality and works for the purpose intended. The regulatory system also imposes rigorous standards on medicines manufacturers and wholesale dealers who trade in them.

The licensing system guarantees accountability for all those involved and ensures that processes, supplies, and quality can be thoroughly monitored and swift corrective action taken where necessary.

The authorisation process for devices differs from that applied to medicines. However, once marketed, safety and performance of medicines and medical devices are monitored and enforced in similar ways.

How is a medicine licensed?

A licence, also referred to as a marketing authorisation, from the MHRA is required before any medicine can be used to treat people in the UK.

To begin the process, companies and/or researchers must apply to the MHRA for permission to test drugs through clinical trials, if these trials are to be conducted in the UK. In order to receive permission to run a trial, they must first satisfy the MHRA that they have met strict safety criteria.

All the test results from these trials on how well the medicine works and its side effects, plus details of what the medicine contains, how it works in the body, and who it is meant to treat, are then sent to the MHRA for detailed assessment.

The assessment team is made up of experts from different relevant specialties, each of whom has undergone additional training in medicines assessment.

The length of the assessment process depends on the type of medicine as well as the quality of the initial information supplied by the manufacturer, how much further detail is required, and how soon queries can be resolved.

In the past, all this information used to be supplied in paper format; now it is supplied electronically, to minimise procedural delays. The MHRA also has to comply with strict timeframes and performance targets for the licensing of medicines.

Once the MHRA is satisfied that the medicine works as it should, and that it is acceptably safe, it is given a marketing authorisation or product licence.

The pharmaceutical company and any wholesalers must also be able to satisfy the MHRA that the manufacture, distribution, and supply of the medicine meet the required safety and quality standards.

Most new types of medicine are licensed by the EMEA, to ensure that it is available to, and used in the same way, across all the member states of the European Union (EU). The breast cancer treatment Herceptin and the antiviral medicine Tamiflu are some examples.

Sometimes the MHRA will be asked to take the lead on the licensing process in Europe, particularly for biological and biotechnology treatments, such as gene therapies. This is an area in which the MHRA has already developed considerable expertise.

Monitoring new medicines and vaccines

New chemicals and vaccines are effectively put on probation for up to two years and labelled with a black triangle to ensure prescribers are aware of the need to monitor them carefully.

The black triangle symbol accompanies new medicines and vaccines in prescribing manuals, product information, and advertising material. It prompts healthcare professionals to report any potential side effects to the MHRA.

This information helps to build up a broader picture of how the treatment works in the general population and enables the MHRA to act promptly, should a previously unrecognised and serious side effect come to light. The black triangle may also be assigned to a medicine that has already been licensed if it contains a new combination of active chemicals or if it is being used in a new way or for a different condition.

The black triangle is not removed until the MHRA is satisfied that the medicine works safely in large numbers of people. Additionally, the MHRA also asks manufacturers to keep a close watch on side effects that may be associated with newly marketed products.

There are around 20,000 different medicines available in the UK.

There are some 80,000 different types of devices and pieces of equipment used in UK hospitals, GP surgeries, residential care, and in patients' homes.

How are devices authorised?

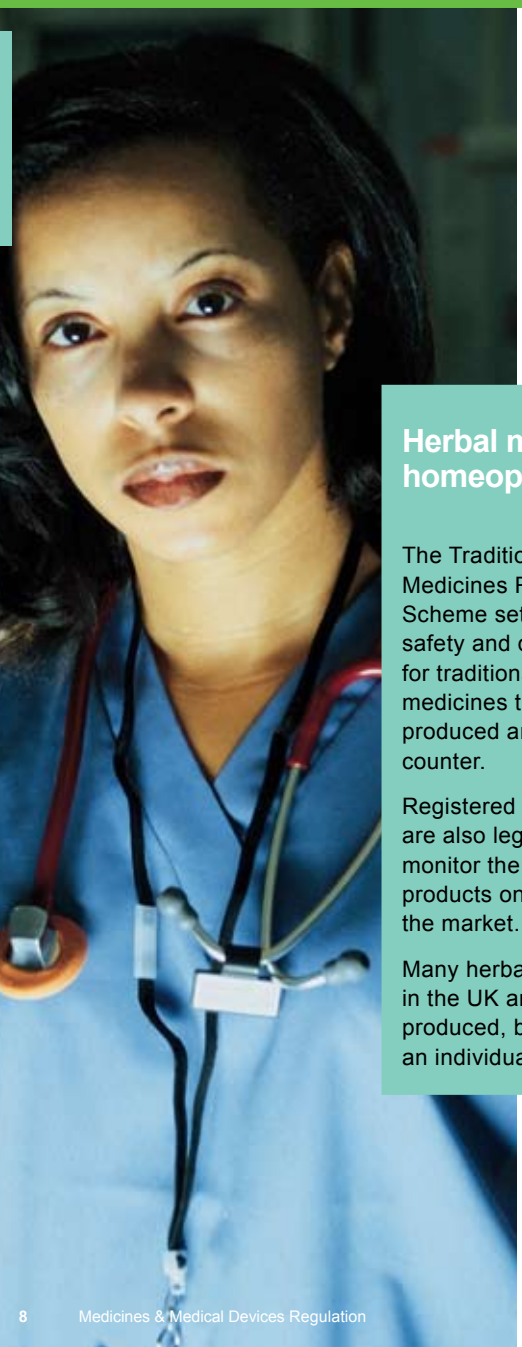
The number and range of medical devices is vast and includes most healthcare products other than medicines used for the diagnosis, prevention, monitoring and treatment of disease, injury, or disability. This means everything from artificial hips to wound dressings, incubators to insulin injectors and scanners to scalpels.

In general, a medical device cannot be marketed in Europe without carrying a CE marking. A CE marking is applied by the manufacturer and means that the device meets the relevant regulatory requirements and, when used as intended, works properly and is acceptably safe. For all but the very lowest risk devices, such as unmedicated bandages, this must be verified by an independent certification body, called a Notified Body, before the CE marking can be affixed. The MHRA is responsible for appointing UK Notified Bodies and regularly audits them to ensure that they perform to high standards.

Manufacturers should be able to support their performance claims for the device. In many cases, and in particular for higher risk devices, this ▶

The MHRA licenses / authorises:

- Pharmaceutical manufacturers
- Medicine importers
- New biological or chemical compounds
- Different brands of existing medicines
- Generics (identical but cheaper versions of existing branded medicines)
- New forms of existing medicines, such as syrups, patches, or injections
- New uses for existing medicines, such as different patient groups or different conditions
- Reclassification of medicines from prescription only to over the counter use, such as the cholesterol lowering medicine Simvastatin (Zocor Heart-Pro)
- Traditional herbal medicines sold over the counter that meet required safety and quality standards
- Designated authorities (Notified Bodies) that approve the quality marking system (CE marking) for medical devices /equipment
- Clinical trials of both medicines and devices, from toothpaste to gene therapy
- Blood banks that meet required safety and quality standards
- Applications on humanitarian grounds to use certain medical devices in the UK not carrying a CE marking



information will come from a clinical trial. Where a manufacturer plans to carry out a clinical trial in the UK, agreement must be obtained from the MHRA. On average, the Agency refuses one in five such requests on the grounds of patient safety or health policy restrictions.

Each year the MHRA receives around 25,000 applications to change the use or format of a medicine.

Herbal medicines and homeopathic remedies

The Traditional Herbal Medicines Registration Scheme sets out specific safety and quality standards for traditional herbal medicines that are mass produced and sold over the counter.

Registered manufacturers are also legally obliged to monitor the safety of their products once they are on the market.

Many herbal remedies used in the UK are not mass produced, but made up on an individual basis, and these are currently exempt from the need for a licence. The MHRA is working with herbal practitioners and the government to introduce safeguards for this type of treatment.

Details of any herbal product found to contain potentially harmful ingredients, or which interacts with conventional medicines, are posted on the MHRA website. The Agency has also recently introduced a new scheme for regulating homeopathic remedies.

Why are clinical trials important?

The serious side effects experienced by volunteers taking part in a trial of TGN1412 in March 2006 at Northwick Park Hospital are extremely rare but indicate the importance of thoroughly testing a treatment before widespread use. A medicine may work well in the laboratory, but a clinical trial will find out if it also works well in people and is safe to use. Clinical trials are phased, and may take several years to complete.

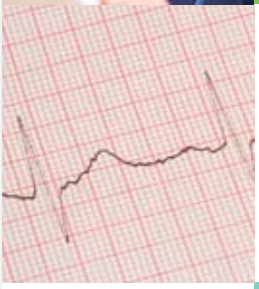
Phase 1 trials usually involve healthy people, and are designed to find out how the medicine works in the body, and whether side effects increase at higher doses. Phase 1 trials often involve fewer than 100 people.

Phase 2 trials look at whether the medicine works in patients with a particular condition or disease and identify common short term side effects. Several hundred people are often involved.

Phase 3 trials gather further information on how well the medicine works and how safe it is, in the general population. And they look in more detail at the range and degree of side effects. The results inform the labelling and patient information for the medicine when it is marketed. Several hundred to several thousand people are often involved at this stage, depending on the type of trial.

Devices are always tested for mechanical and/or electrical safety before they are used in/on people, but, unlike medicines, they are not automatically subject to a clinical trial. This is because it is often impractical and unnecessary to test them in this way and safety and performance can be based on laboratory tests. Whether a device is subject to a clinical trial will depend on the type of device, its intended use, and how 'new' or different it is.

Around 5,000 licences are granted to medicines, manufacturers and wholesalers each year.



How does the MHRA monitor safety and quality standards?

There are several ways in which the MHRA checks the safety and quality standards of healthcare products and ensures that they comply with European and UK law and regulations. Inspections, reporting systems, and intelligence about illegal activity all have key roles.

As well at its own inspection teams and proactive monitoring, the MHRA relies on manufacturers, healthcare professionals, and the public to report defects, side effects, and misleading information.

The MHRA monitors safety and quality standards by:

1 Regular inspections of good and safe practice, including:

- Medicines manufacture and supply
- Medicines distribution and storage
- Clinical trials
- Auditing of clinical inspecting system for devices
- Laboratories testing medicines
- Auditing Notified Bodies
- Inspection of blood establishments.

2 Annual routine sampling of around 3,000 marketed medicines at manufacturers' premises, wholesalers, and pharmacies, proactive medical device programme.

3 Publishing standards on ingredients and expected quality for medicines (British Pharmacopoeia).

4 Ongoing reports from healthcare professionals, patients, and manufacturers, including:

- Potential side effects of prescription and over the counter medicines and herbal remedies (Yellow Card Scheme)
- Design faults / poor instructions or maintenance / incorrect use of devices (Adverse Incident Reporting Scheme)
- Defective medicines
- Serious side effects involving blood and blood components (SABRE).

5 Reviews of important new evidence on products, such as antidepressants (SSRIs) or hormone replacement therapy (HRT), or implantable defibrillators, a device used to correct irregular heart rhythms.

6 Commissioning research into medicines safety and supporting Department of Health Research & Development initiatives into innovative medical device technology and technology related procedures.

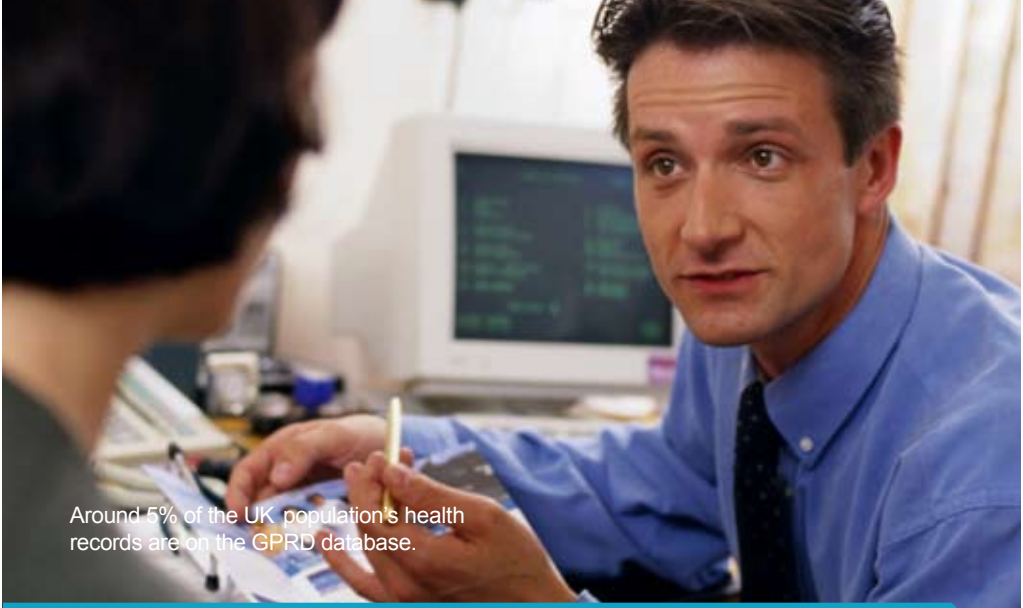
7 Assessment of misleading or incorrect information, including:

- Adverts
- Product labelling
- Product information leaflets.

8 Gathering intelligence about illegally manufactured imported and counterfeit medicines and medical devices.

9 Managing the General Practice Research Database (GPRD), information from which is used to detect healthcare trends and monitor the safety and risk benefit of market licensed medicines.

10 Legally enforcing regulations and statutory obligations, including checking on products that are not licensed as medicines or medical devices.



Around 5% of the UK population's health records are on the GPRD database.

Why is the General Practice Research Database important?

The government entrusts the MHRA to manage the General Practice Research Database (GPRD). The GPRD is an internationally recognised database which is used to research safety and effectiveness issues of licensed medicines as well as improve the understanding of disease. The database contains the anonymised records of patients registered at more than 480 family doctor (GP) practices across the UK, and is the largest/most validated population based database of its kind in the world, detailing illness, investigations, and treatment. Patients can opt out of allowing their records to be used in this way, and all access to the data and research is strictly controlled.

The GPRD dataset is regularly updated and used by academics, pharmaceutical companies, and regulators. It enables them to ensure that medicines in everyday use are acceptably safe and effective. The GPRD is used hand in hand with data from the Yellow Card Scheme as part of an overall warning system for medicines.

Nearly 500 studies have been published, based on the anonymised information contained in the records. For instance the database has been used to investigate whether there were serious side effects associated with common treatments, including the Pill, MMR, antidepressants, and hormone replacement therapy. It is currently being used to assess the safety of non-steroidal inflammatory drugs, such as aspirin and ibuprofen.

More information on the GPRD is available at: www.gprd.com

A patient's view of the Yellow Card Scheme

(reporting system for possible side effects related to medicines)

'Patients get very worried about the side effects they experience, and they need to know if they are normal or not. When I took Roaccutane (for acne) I had excessively dry lips, eyes, and nose, and I had flare-ups of acne. It was very distressing.

Being able to report side effects through the Yellow Card Scheme puts you in control. It means that you can report directly without having to wait for a busy healthcare professional to do it.

Patients might not want to bother reporting side effects, but I think they should. The information goes back to pharmaceutical companies, so it can make a difference. And it's easy to do and clearly explained. You can call or do it online.

It's about putting patients at the centre of care. It's a quantum leap for patient involvement, and marks the beginning of the way forward and a sea change in attitude.'

- Alison Bowser

Patients can use the Yellow Card Scheme for themselves, and on behalf of a child or adult in their care.

Call 0808 100 3352 to report by phone, or go to www.mhra.gov.uk to download a report form for posting, or fill it in online.

The Yellow Card Scheme receives more than 20,000 reports of possible side effects each year.

Half a million reports were received in the scheme's first 40 years.

What happens when quality or safety concerns arise?

When a product is suspected or known to be faulty, the MHRA immediately works with manufacturers and wholesalers on the most appropriate and timely action to take. Sometimes this means a product has to be recalled and taken out of the supply chain.

By law, manufacturers must report to the MHRA any important defects in both medicines and medical devices.

The action taken is determined by the scale of the threat posed to the public's health. The MHRA is committed to responding promptly and appropriately to concerns.

Reports prompt investigations, which can result in the issue of warnings and alerts. The MHRA also has the power to prosecute when regulations have been breached. The courts can impose fines or prison sentences when the law has been broken. And the Agency can withdraw unlicensed/ illegal products from the market.

Warnings (Alerts) can be issued about defective medicines, problems with devices, and side effects associated with medicines and blood and blood products.

These are sent out to healthcare professionals and organisations, and publicised widely in print and online, including on the MHRA website.

Dealing with faulty medicines

The MHRA's Defective Medicines Report Centre (DMRC) issues alerts to healthcare professionals, hospitals, GP surgeries, and wholesalers to tell them when a medicine is being recalled or when there are concerns about the quality that will affect its safety or effectiveness.

These alerts are graded according to the seriousness of the threat to the public's health:

Class 1 requires immediate recall, because the product poses a serious or life threatening risk to health.

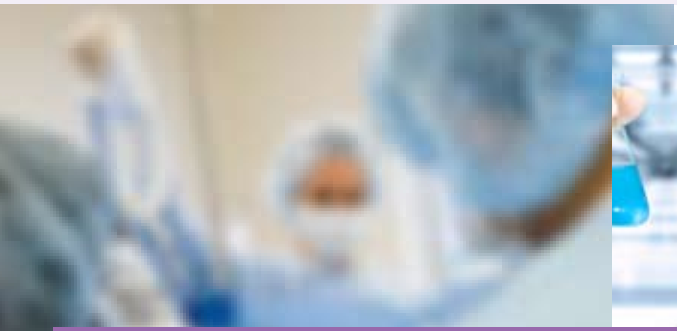
Class 2 specifies a recall within 48 hours, because the defect could harm the patient but is not life threatening.

Class 3 requires action to be taken within 5 days because the defect is unlikely to harm patients and is being carried out for reasons other than patient safety.

Class 4 alerts advise caution to be exercised when using the product, but indicate that the product poses no threat to patient safety.

Most recalls fall into classes 2 or 3.

Counterfeit medicines were found in the legitimate supply



In 2007, more than 500 defects related to medicines were reported to the MHRA, resulting in the issue of more than 30 Drug Alerts.

chain in 2007 resulting in several Class 1 alerts. These included Plavix tablets, Zyprexa tablets, Casodex tablets and Sensodyne toothpaste. These products included parallel-imported and parallel-distributed items. Samples were tested in the original manufacturers' laboratories and the Agency laboratory to determine the risks to the patient.

While warnings about side effects are issued and changes to the prescribing indications or doses made for licensed medicines, few medicines are withdrawn from use. That is because most work well and are acceptably safe.

In 2007, lumiracoxib (Prexige), a medicine used to treat painful symptoms of osteoarthritis was withdrawn from the UK market. This followed a review of the balance of risks and benefits of the drug; in particular concerns relating to worldwide data on spontaneously-reported cases of serious liver toxicity associated with lumiracoxib.

The MHRA carries out around 1000 inspections on pharmaceutical manufacturers and wholesalers each year.

Responding to concerns about devices

Healthcare professionals and their patients, as well as manufacturers, can report problems about devices to the MHRA's adverse incident reporting scheme. These reports help manufacturers improve their design and product information, and they also help the MHRA improve the safety of devices.

All reports are assessed, and acted on although the response will be graded, according to the seriousness of the incident and/or the potential for future harm. Further information is obtained before we determine our response, which may be:

- a Medical Device Alert, giving advice to the healthcare service, and/or
- a requirement for the manufacturer to make appropriate changes in design or information, or
- a product recall, or
- sending the data to the manufacturer and storing it in MHRA's database to help us spot trends that require action

Sometimes the instructions for use or labelling are unclear. Sometimes, patients and healthcare practitioners simply do not use a device or piece of equipment in the way in which the manufacturers intended.

Each year the MHRA receives around 8000 device reports. 79 Alerts were issued in 2007, some of which were serious enough to warrant immediate action. Some of the products investigated included pacemakers, powered wheelchairs, and blood sample collection tubes. More than 400 manufacturer field safety corrective actions were monitored by MHRA, and over 800 improvements were made to the design and manufacturing process.

The number of device reports has risen over the past decade. Technology has become more complex and sophisticated, and patients and professionals have been encouraged to report problems. The number of devices in use has also increased significantly over this period.

Increased reporting also reflects a high level of awareness and therefore the effectiveness of the safety monitoring system. It does not mean that manufacturing standards have fallen or that devices have become less safe, overall.

The MHRA devices user reporting system is among the largest of its kind in the world.

How device reporting makes a difference

The MHRA brought together an expert group to look at silicone gel breast implants after an increase in safety concerns. The expert group concluded that silicone implants were safe to use. However, the MHRA found that this was not the case for certain other types of breast implants.

These were taken off the market and information posted on the website about the implant options for women considering breast implants.

In another case, the MHRA was the first regulator in the world to pick up a problem with a particular heart valve after a UK surgeon raised concerns about its safety.

The MHRA investigated and found that the high complication rate associated with the valve was attributable to a design change. The manufacturer took the product off the market.

The public can also play its part. A coroner advised the MHRA that a urinary catheter intended for use in women had inadvertently been used in a man, contributing to his death. Anxious to prevent this happening again, the coroner asked if the labelling of the catheters could be revised to distinguish them more clearly.

The MHRA accordingly wrote to all the relevant manufacturers, and their trade association, requesting that the catheters also be clearly labelled, so that it would be easy to distinguish between them once removed from the packaging. Advice was also published for healthcare professionals, prompting them to double check the labelling.

If you have a concern about a device, our preference is that you report it online at www.mhra.gov.uk. Alternatively you can email the MHRA at aic@mhra.gsi.gov.uk or phone on +44 (0)20 3080 7080.

Is it safe to order medicines and devices over the internet?

UK high street pharmacies have to be registered with the pharmacists' regulatory body, the Royal Pharmaceutical Society of Great Britain (RPSGB).

While many registered pharmacies have online facilities and work within the law, unregistered outfits are also operating on the Internet. A UK web address (.co.uk) is no guarantee that the pharmacist is working out of the UK and/or registered with the RPSGB.

It is therefore impossible to guarantee the quality or effectiveness of all prescribed medicines ordered online, and especially those ordered without a prescription. The Internet is one of the sources of the increasing trade in fake or counterfeit medicines and devices.

These include antibiotics, slimming aids, anti-malarial pills, treatments for erectile problems, such as Viagra and Cialis, and recently, the cholesterol lowering medicine Lipitor. The World Health Organisation estimates that fake medicines already make up more than 10 per cent of the global medicines market.

The Internet is also a source of illegally marketed medicines, such as ketamine, an anaesthetic used in animals, marketed as a recreational drug, and ephedrine, a nervous system stimulant, marketed as a dietary supplement or sports aid.

Devices, such as heart valves, glucose meters, and cholesterol checking kits are also available on the Internet. Again, the quality and safety of these products is unknown.

The MHRA has been very active in tracking down counterfeit and illegal products and has seized consignments and prosecuted manufacturers and importers. But it is an increasingly lucrative and growing market.

Influencing Policy

As well as operating the current regulatory system, the MHRA works to influence the shape of future regulation. As new technologies, such as tissue engineering and genetics start to offer new treatment possibilities, the Agency is helping to design and implement new safeguards, usually through new EU legislation.

The Agency was a leading contributor to new EU rules, which will greatly improve the availability of medicines suitable for children—an area previously neglected in medicines development.

The MHRA works with the Department of Health to ensure that regulation supports wider healthcare policies. This includes helping patients to make more informed choices about medicines through better labelling and information; and making it easier for people to get the medicines they need, by making more medicines available over the counter, and enabling suitably trained nurses and pharmacists to prescribe medicines.

The MHRA has a wide range of international links, and is respected as one of the leading regulatory authorities for medicines and medical devices worldwide. The Agency has shared its regulatory expertise with Malta, Latvia and the Czech Republic, in a bid to help countries that have recently joined the EU to develop the systems needed to play an active part in European regulation.

The Agency has been working with professional education and training bodies in the UK to raise awareness of the importance of regulation and safe use of products in medical training and continuing professional development programmes. The MHRA is working on an accreditation scheme with the medical Royal Colleges to grant the equivalent of a ‘driving licence’ for the safe use of particular pieces of equipment for different specialties.

If you are a patient, healthcare professional, or work for a pharmaceutical company or medical device manufacturer and would like more information on the work of the MHRA, including various publications, or if you would like to know how you can contribute to the safe use of medicines, medical devices and equipment, please contact:

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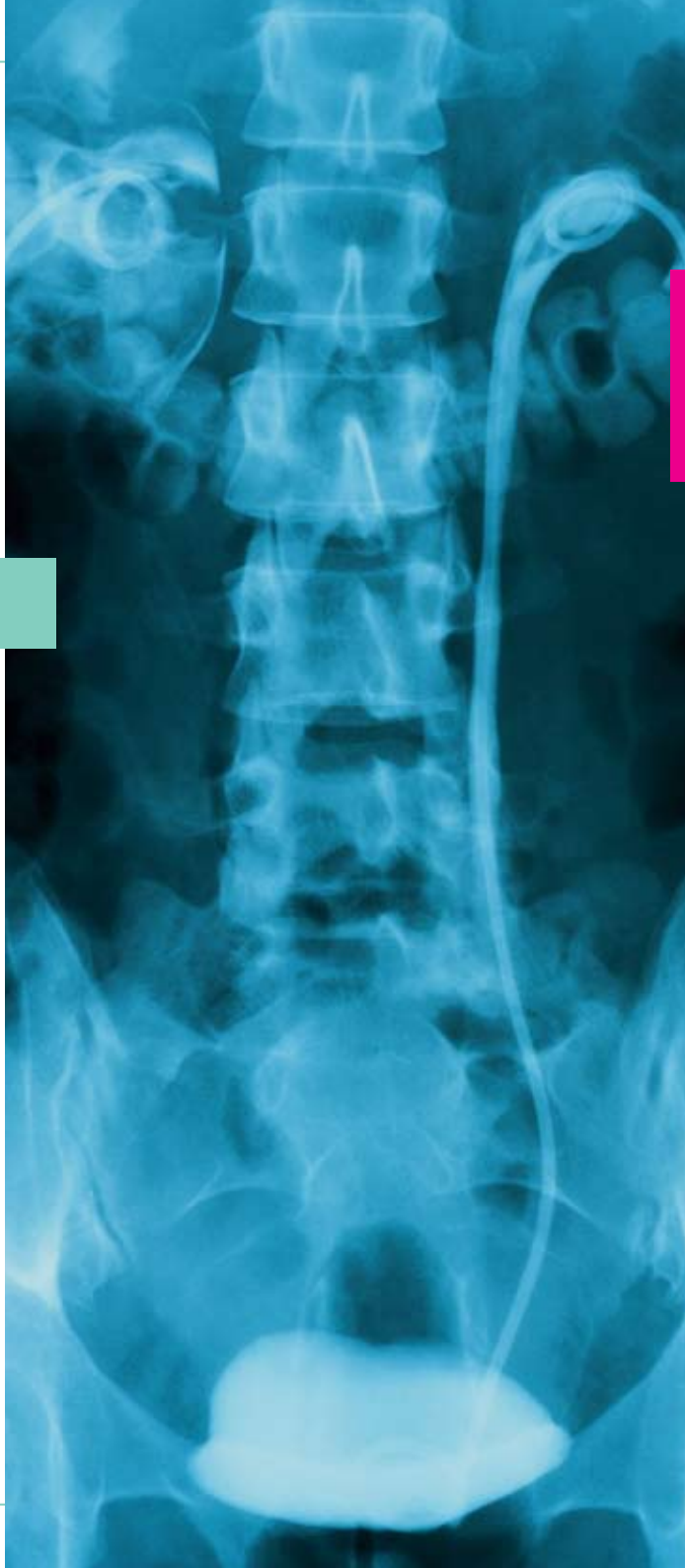

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Revised and updated April 2008