

MHRA

Medicines and Healthcare products Regulatory Agency

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The MHRA was set up in April 2003 from a merger of the Medicines Control Agency and the Medical Devices Agency. The MHRA is the government agency which is responsible for ensuring that medicines and medical devices work, and are acceptably safe.

The MHRA's aims and objectives

Aims

- Protecting public health through regulation, with acceptable benefit-risk profiles for medicines and devices.
- Promoting public health by helping people who use these products to understand their risks and benefits.
- Improving public health by encouraging and facilitating developments in products that will benefit people.

MHRA's strategic objectives are to:

- Safeguard public health through MHRA's primary role in ensuring that the products MHRA regulate meet required standards, that they work and are acceptably safe;
- Carry out communication role through the provision of accurate, timely and authoritative information to healthcare professionals, patients and the public;
- Support research, ensuring through the application of Better Regulation principles that regulation does not stifle innovation;
- Influence the shape of the future regulatory framework through use of our effective European and International relationships;
- Run an organisation with a skilled and equipped workforce that is fit for the future.

The MHRA's activities

- Assessing the safety, quality and efficacy of medicines, and authorising their sale or supply in the UK for human use.
- Overseeing the UK Notified Bodies that audit medical device manufacturers.
- operating post-marketing surveillance and other systems for reporting, investigating and monitoring adverse reactions to medicines and adverse incidents involving medical devices and taking any necessary action to safeguard public health, for example through safety warnings, removing or restricting the availability of products or improving designs.
- Operating a proactive compliance programme for medical devices.
- Operating a quality surveillance system to sample and test medicines and to address quality defects, monitoring the safety and quality of imported unlicensed medicines and investigating Internet sales and potential counterfeiting of medicines.
- Regulating clinical trials of medicines and medical devices.

- Monitoring and ensuring compliance with statutory obligations relating to medicines and medical devices through inspection, taking enforcement action where necessary.
- Promoting good practice in the safe use of medicines and medical devices.
- Managing the General Practice Research Database (GPRD) and the British Pharmacopoeia (BP) and contributing to the development of performance standards for medical devices.
- Offering scientific, technical and regulatory advice on medicines and medical devices.
- Providing the public and professions with authoritative information to enable informed dialogue on treatment choices.

MHRA's structure:

Corporate governance

- 1) **The Agency Board** is made up of a non-executive Chairman, six non-executive members and the Agency's Chief Executive Officer who is responsible for service delivery and resources.
- 2) **The Executive Board** consisting of the Agency's directors takes overall responsibility for day-to-day management, strategic decision-making, line management, and all financial, policy, operational and resource management issues.
- 3) **The Risk and Audit Committee** provides independent feedback to the Chief Executive and the Management Board on the effectiveness of risk management processes.

The MHRA's main activities are supported by ten Divisions:

1. Licencing division
2. Vigilance Risk Management of Medicines (VRMM)
3. Device Technology& Safety
4. Devices Clinical
5. Inspection, Enforcement and Standards
6. Information Management
7. Human Resources
8. Operations and Finance
9. Policy
10. Communications

What MHRA regulates?

Medicine

Device

Advanced therapeutic medicinal product

Nanotechnology

Blood

Medicine

- ◆ Licencing of medicines
- ◆ Medicines for children
- ◆ Inspection and standards
- ◆ Importing and exporting medicines
- ◆ Best practice guidance on labelling and packaging of medicines
- ◆ The safety of medicines

How MHRA regulates medicines?

All medicines available in UK are subject to rigorous scrutiny by MHRA before they can be used by patients

The Medicines Act:

- Introduced a number of other legal provisions for the control of medicines
- Provided a comprehensive system of licensing affecting manufacture, sale, supply and importation of medicinal products

The role of MHRA:

- Assess applications for marketing medicinal products
- Assess applications to undertaken clinical trials
- Inspect the manufacturers and wholesalers of medicines-licensing
- Undertake post-marketing surveillance including:
 - Pharmacovigilance
 - Quality defect monitoring
 - Sampling and testing
 - Product recalls.
- Issue certificates to companies wishing to export their medicinal products to countries outside the EU.
- Enforce the statutory requirements covering medicines control and good clinical practice guidelines.
- Publish quality standards for drug substances through the "British Pharmacopoeia".

Licensing of medicines

- Before a medicine can be sold in the UK, a number of licences are essential. The product itself must have a licence called a 'marketing authorisation' (formerly called a 'product licence').
- In addition, the companies that are involved in all stages of the manufacture and distribution of the product need to have licences (manufacturer's and wholesale dealer's licences). New products which are still in development also need a licence before they can be tested on human subjects (clinical trial authorisations).
- Types of license:

Manufacturer's and Wholesale Dealer's licences

| <u>License type</u> | <u>Licensed activity</u> |
|--|---|
| Human products | |
| Manufacturer's/Importer's License (MIA) | Allows the holder to: <ul style="list-style-type: none">➤ manufacture and/or assemble (package) medicinal products➤ wholesale deal licensed medicinal products imported from countries outside the EEA |
| Manufacturer 'specials' License (MS) | Allows the holder to: <ul style="list-style-type: none">➤ manufacture unlicensed medicinal products (commonly referred to as 'specials')➤ import unlicensed medicinal products from outside the EEA |
| Manufacturer investigational medicinal products (MIAIMP) | Allows the holder to manufacture investigational medicinal products used in |

| | |
|---|---|
| | clinical trials |
| Full Wholesale Dealer License (WL) | Allows the holder to wholesale deal pharmacy (P), prescription only (POM) and General Sale List (GSL) medicines |
| Wholesale Dealer (GSL) License (WDL) | Allows the holder to wholesale deal General Sale List (GSL) medicines only |
| Veterinary products | |
| Manufacturer's/Importer's Authorisation (ManA) | Allows the holder to: ➤ manufacture and/or assemble (package) medicinal products ➤ wholesale deal licensed medicinal products imported from countries outside the EEA |
| Manufacturer 'specials' Authorisation (ManSA) | Allows the holder to manufacture unlicensed medicinal products (commonly referred to as 'specials') |
| Wholesale Dealer Authorisation (WDA) | Allows the holder to wholesale deal (POM-V), (POM-VPS), (NFA-VPS), AVM-GSL) medicines |

Renewals and variations to licenses (Marketing authorisation)

Marketing authorisations are granted for periods up to five years and have to be renewed at the end of this time.

Medicines that do not need a licence (Exemptions from licensing)

- The manufacture and supply of unlicensed relevant medicinal products for individual patients ('specials')
- The importation and supply of unlicensed relevant medicinal products for individual patients
- Herbal remedies exemptions

The manufacture and supply of unlicensed relevant medicinal products for individual patients ('specials')

- Some patients may have special clinical needs that cannot be met by licensed medicinal products. So that these special needs may be met, the law allows manufacture and supply of unlicensed medicinal products (commonly known 'specials') subject to certain conditions.
- Examples of "special needs" include an intolerance or allergy to a particular ingredient, or an inability to ingest solid oral dosage forms.
- "special" may only be supplied to third parties if all of the following apply:
 1. There is a bona fide unsolicited order;
 2. The product is formulated in accordance with the requirement of a doctor, dentist or supplementary prescriber registered in the UK;
 3. The product is for use by his individual patients on his direct personal responsibility;
 4. It is produced and supplied under specific conditions.

Persons authorised to procure "specials"

- (a) Doctors or dentists registered in the UK;
- (b) Supplementary prescribers (e.g. an appropriately qualified nurse or pharmacist)

- (c) Pharmacists in hospitals, health centers or registered pharmacies;
- (d) Licensed wholesale dealers for supply to the order of any of the above;
- (e) Licensed manufacturers for import for supply to the order of any of the above.

- If a 'special' is manufactured in the UK, the manufacturer must hold a manufacturer's (specials) license issued by the MHRA. A 'special' may not be advertised and may not be supplied if an equivalent licensed product is available which could meet the patient's needs.

Importation into the UK

- (a) A wholesale dealer's licence if the product is to be imported from an EEA member state i.e. the EU plus Norway, Iceland and Liechtenstein, or
- (b) A manufacturer's ("specials") licence if the product is to be imported from a third country i.e. a non-EEA country

The importation and supply of unlicensed relevant medicinal products for individual patients

Herbal remedies exemptions

Products exempt from licensing include herbal medicines which satisfy the conditions laid down in Section 12 of the Medicines Act 1968.

Section 12 (2) allows the manufacture, sale or supply of herbal remedies where:

- the process to which the plant or plants are subjected consists only of drying, crushing or comminuting;
- the remedy is sold without any written recommendation as to its use; and
- The remedy is sold under a designation which only specifies the plant(s) and the process, and does not apply any other name to the remedy.

The UK Parallel Import Licensing

- The UK Parallel Import Licensing Scheme allows medicinal products authorised in other EU Member States to be marketed in the UK. The granting of licenses in the EU for such a purpose began in 1984.
- **Parallel import licence application categories**
- From 1 April 2009 Parallel Import License applications are in one of three categories:
- **Parallel import (simple):** This category will apply when the UK product and the product to be imported from a Member State are manufactured by companies in the same group of companies or are made under license from the same licensor.
- **Parallel import (standard):** This category will apply when the UK and imported products do not share a common origin (as defined above) and the application is not 'Complex'
- **Parallel import (complex):** This category will apply when the UK and imported products do not share a common origin (as defined above) and:
 - a. the imported product contains a new excipient
 - b. the imported product contains an active ingredient made by a different route from that used in the UK product
 - c. the imported product is a controlled release preparation
 - d. the imported product is a sterile product which is sterilised in a different way from the UK product
 - e. the imported product is a sterile product in which the container is made from a different material to the container of the UK product

- f. the imported product is an influenza vaccine
- g. the product is a metered dose inhaler
- h. the product is a powder for inhalation
- i. bioequivalence of the UK and imported product cannot be demonstrated through bioavailability studies
- j. the sole or primary evidence for the safety and efficacy of the imported product consists of published scientific literature
- k. The manufacturer of the active ingredient contained in the imported product is different from the manufacturer of the active ingredient contained in the UK product.

For the standard and complex categories, companies will be required to submit suitable pharmacovigilance plans with the application.

Importing unlicensed medicines

The Medicines Act contains certain important exemptions from licensing. One of these exemptions is for the importation and supply of unlicensed relevant medicinal products for individual patients and herbal remedies exemptions.

Exporting medicines

- The MHRA, on behalf of the Department of Health, issues export certificates on request to assist exporters of medicinal products to satisfy the import requirements of other countries.
- The certificates issued by MHRA indicate whether the product or manufacturer to which the certificate applies has met statutory requirements.

Information on types of export certificates

The MHRA issues four different types of export certificates, two of which comply with the format established by the WHO. Each type of certificate is country specific, naming one individual country - the EU is not acceptable as a one-country unit.

1) Certificate of a pharmaceutical product (CPP).

- This certificate complies with the format specified by WHO. The certificate will provide details about a single named medicinal product which may be licensed or unlicensed in the UK.
- It provides details about the product and its manufacture including (but not limited to) the marketing authorisation (MA) holder, the active ingredients and excipients, the manufacturing and packaging sites and whether or not the product is placed on the market in the UK.
- For the MHRA to issue a certificate to an applicant other than the marketing authorisation holder written permission from the marketing authorisation holder will be required before the application can be accepted.

2) Certificate of licensing status (CLS).

- This certificate complies with the format specified by the WHO. It is intended for use by importing agents who are required to screen bids made in response to an international tender and can apply to licensed or unlicensed products.
- It provides less information than the CPP and can include a maximum of ten products per certificate.

3) Certificate of manufacturing status (CMS)

It does not provide any product specific information, but it confirms whether named sites meet Good Manufacturing Practice (GMP) requirements on a specified manufacturing licence number. All or any of the sites named on the manufacturing licence may be listed on the certificate.

4) Certificate for the importation of a pharmaceutical constituent

- (CPC) is available for a named constituent of a medicinal product. The MHRA will only issue certificates for unlicensed medicinal products that are manufactured in the UK on a site holding a manufacturer's licence appropriate to the dosage form of the product for which the certificate applies.
- If an application is made for a certificate for a medicinal product that is not manufactured in the UK it will only be issued if the product has a UK (not EMEA) product licence. It is not possible to issue a certificate for unlicensed products manufactured outside the UK.

Legal status and reclassification

- Legal status of medicinal product is a part of the marketing authorizations and products may be available either on a prescription (prescription only medicines (POMs), or available in a pharmacy without prescription, under the supervision of a pharmacist (P) or on general sale (GSL).

Reclassification the criteria

Criteria for switching from POM to P

Before a medicine can be switched from POM to P, Ministers must be satisfied that it would be safe to allow it to be supplied without a prescription. This means that it is a medicine which no longer meets any of the following criteria (Medicines Act 1968, section 58A) and that it is a medicine which:

1. Is likely to present a direct or indirect danger to human health, even when used correctly, if used without the supervision of a doctor; or
2. Is frequently and to a very wide extent used incorrectly, and as a result is likely to present a direct or indirect danger to human health; or
3. Contains substances or preparations of substances of which the activity requires, or the side effects require, further investigation; or
4. Is normally prescribed by a doctor for parenteral administration.

Criterion for switching from P to GSL

Similarly, before a medicine can be switched from P to GSL, Ministers must be 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).

Reclassification procedures

- New medicines are usually authorised for use as prescription only medicines (POM). After some years' use, if adverse reactions to the medicine are few and minor, it is possible that the medicine may be safely used without a doctor's supervision. If there is sufficient evidence of safety, a medicine may be reclassified for sale or supply under the supervision of a pharmacist (P).

- Pharmacy medicines which have been safely used for several years may be suitable for general sale and may be reclassified as GSL.
- The MHRA has introduced a new process by which medicines are reclassified from POM to P and P to GSL. Applications may be made at any time during the year with a target timescale for their determination.
- Less frequently, medicines, which were previously classified as P, are made POM if new risks are identified which require involvement of a doctor to ensure safe use of the medicine. In the same way a GSL medicine could be reclassified P if new information showed that it was no longer safe to supply it without a pharmacist checking that it was suitable for the patient.
- The MHRA Guidance Note 11, 'Changing the legal classification in the United Kingdom of a medicine for human use' covers reclassification from POM to P and P to GSL.

POM to P (Prescription only medicine to pharmacy)

Orlistat, Tamsulosin hydrochloride, Alclometasone dipropionate, Pantoprazole, Domperidone maleate

P to GSL (Pharmacy to general sale list)

Loratadine, Terbinafine hydrochloride, Nicotine, Salicylic acid, Dimeticone, Nicotinamide, Benzocaine

Medicines for children

- There are comparatively few medicines on the market which are specifically licensed for the treatment of children or are available in suitable formulations.
- Specific clinical trials in paediatric populations are normally required due to age-related differences in the drug handling or drug effects which may lead to different dose requirements to achieve efficacy or to avoid adverse effects.
- For it CSM Pediatric Medicines Working Group was established in July 2000. In September 2004 the European commission published a proposal.
- The main objective of the proposal includes:
 1. Increased availability of medicines specifically adapted and licensed for use in the pediatric population
 2. Increased information available to the patient/carer and prescriber about the use of medicines in children, including clinical trial data
 3. Increase high quality research into medicines for children

Best practice guidance on labelling and packaging of medicines

The primary purpose of medicines labeling and packaging is the clear unambiguous identification of the medicine and the conditions for its safe use.

The purpose of this guidance

- To expand a set of principles which have been agreed by the Committee on Safety of Medicines.
- To help to ensure that the critical information necessary for the safe use of the medicine is legible, easily accessible and that users of medicines are assisted in assimilating this information so that confusion and error are minimised.

General considerations

Label must contains

- Name of the medicine
- Expression of strength (where relevant)
- Route of administration
- Posology
- Warnings

- These critical items of information should be located together on the pack and appear in the same field of view where practicable.
- These items should not be broken up by additional information, logos or background texts or graphics.
- The critical information should appear in as large a font as possible to maximise legibility, on at least one face of the presentation.

Name of the medicine

- The full name of the medicine should appear on at least three non opposing faces of the pack to aid accurate identification of the drug.
- Where the common name appears after the brand name, it should be given due prominence. Generally this will be determined by the relative size of the text but other factors may be relevant such as colour of text and the font used.

Expression of strength

- It may be necessary in some cases to express the strength as quantity per unit volume and also as the total quantity per total volume. Reference to the total quantity per total volume should be highlighted.
- This is particularly important for injectable products and other medicines available in solution or suspension.
- For safety reasons it is important that micrograms is spelt out in full and not abbreviated.

Route of administration.

- This should be as registered in the SPC only.
- Some routes of administration will be unfamiliar to patients and may need careful explanation.

Posology

- Posology remains a legal requirement for products marketed for retail sale. In general, posology will not appear on medicines that are intended to be supplied on prescription.
- **Innovative pack design** that may incorporate the judicious use of colour is to be encouraged to ensure accurate identification of the medicine.
- Only positive statements should appear on medicines labelling to avoid ambiguity of the message.
- Where practicable, packs should include space for the placement of the dispensing label. It is recommended that this should be a blank white space in which there is no text of any kind, to aid legibility of the dispensing label

Small Containers

- The criteria for small container status would normally be considered to apply to containers with a nominal volume of 10mls or less.
- The critical items outlined above are not additional requirements here.
- For traceability purposes it is recommended that the following additional information should appear on the labelling of small containers:

- PL number
- The MA holder's name.

Blister packaging

- Where practicable, the name and strength of the product should appear over each blister pocket or be oriented centrally across the pack. In all cases it will be acceptable to apply the batch number and expiry date to the end of the blister strip.
- In addition, blister foils should be printed to ensure maximum legibility of the statutory information using a sufficiently large font.

Inspection and standards (Ensuring the quality of Medicines)

- Inspection of research, development and quality control laboratories, clinical trials, manufacturers, wholesalers and pharmacovigilance systems is carried out by the Inspectorate Group of the Inspection and Standards Division.
 1. Good manufacturing practice Medicine Inspectorate
 2. Good Distribution Practice (GDP) Medicine Inspectorate
 3. Good Laboratory Practice (GLP) Monitoring Authority
 4. Good Clinical Practice (GCP) Inspectorate
 5. Pharmacovigilance (GPvP) Inspectorate

Good manufacturing practice (GMP)

Ensures that medicinal products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization (MA).

Certain information related to activities of inspectorate:

When is inspection carried out?

Whenever a company has applied for a manufacturer's or wholesale dealer's license and periodically during the course of a license

What is maximum interval for inspection?

Two years- Manufacturers

Four years – Wholesalers

Three years- overseas manufacturers

What is about license and inspection of overseas manufactures?

UK authorities do not license overseas manufacturers but inspection carried out prearranged or unannounced.

What is at the end of inspection?

Written notification is given to the organization on the deficiencies found.

External liaison

- The UK Medicines Inspectorate was a founder member of the Pharmaceutical Inspection Convention and is an active participant in the Pharmaceutical Inspection Co-operation Scheme (PIC/S).
- The GMP Inspectorate currently carries out regular inspections in a number of countries, including USA, India, China and Japan both in connection with national requirements and on behalf of the European Medicines Agency

(EMEA), the World Health Organization (WHO) and the European Directorate for the Quality of Medicines (EDQM).

- For Community marketing authorisations, for example, licences granted under the centralised procedure, initial inspection is carried out under contract to the EMEA. This is normally carried out by the Supervisory Authority concerned, i.e. the Member State in which the product is to be made or imported.
- Subsequent inspections are normally carried out routinely by the same authority although there is provision for one Member State to inspect in non-Member States on behalf of another.

Site Master File (SMF)

- A Site Master File (SMF) is a document that the MHRA requests the licence holder or applicant to provide, that describes the structure of the organisation involved, the site, the manufacturing activities carried out, the facility and premises employed and also details of the quality management system in place.
- The purpose of the SMF is to provide the Inspector with an introduction to the company and its activities prior to the inspection taking place and to demonstrate to the Inspector that the site is ready for the inspection and has put a basic quality system in place.
- The complete SMF should ideally be no more than 25 pages long.
- Process flow charts and drawings are preferred to long narrative descriptions. Where a drawing is recommended the guide will indicate this using the following symbol.

| | |
|---|---|
| Title page | The name of the manufacturing organisation and license holder address, telephone number and key contact details, the name of the author(s), the date of issue, the version number and the date on which revision is due |
| Copy of the current Manufacturing Authorisation (s) | Details of the licenses held and the license number |
| Details of Products manufactured | Details of the pharmaceutical dosage forms, details of any other products handled in the same environment |
| Licensed organisation location | A short description of the location of the facility |
| Licensed Organisation History | Very brief history of how it has evolved |
| Site Drawing and Description | Basic schematic drawings of the various areas: <ul style="list-style-type: none">➤ Production Areas➤ Storage Areas including delivery and dispatch routes➤ Quality Control Labs➤ Office & Administration areas |
| Personnel | Diagrammatic representation of the organisational structure, Details of the number of staff employed in relation to the licensed facility ie in production; quality control; quality assurance and storage and distribution. |
| Responsibilities | Qualifications, experience and responsibilities of each of the management team and any other key members of staff |
| Production | <ul style="list-style-type: none">➤ Description or flow diagram for main processes➤ Equipment used in the process (es). Indicate |

| | |
|-------------------------------------|--|
| | <p>whether it is dedicated to a particular product or multi purpose</p> <ul style="list-style-type: none"> ➤ Batch sizes ➤ Contamination Risks ➤ Final pack presentations ➤ Cleaning ➤ Clothing required in the production areas ➤ Validation policies for Equipment & Facility ➤ Process validation ➤ Calibration and Maintenance of key equipment ➤ GMP related Computerised Systems - including life cycle review ➤ Water system ➤ HVAC system |
| Quality Management system | <p>Describe the elements of the Quality Assurance system and explain how the quality of the products is guaranteed. The following aspects should be included:-</p> <ul style="list-style-type: none"> ➤ How the quality of starting and packaging materials is assured ➤ General Documentation system ➤ Batch records – generation, control and traceability ➤ Written procedures ➤ Analytical results – who reviews them ➤ How are finished product specifications generated ➤ How “Out of Specification” results are handled ➤ Complaints ➤ Deviation reports ➤ Recall procedures ➤ Who takes ultimate responsibility for the quality of the product and its final release? ➤ Self inspection system |
| Training | <p>Give details of how training is undertaken and recorded. Both core staff and ancillary staff are mentioned.</p> |
| Quality Control | <p>Description of routine chemical or microbiological analysis performed and any laboratories on site, name and address of the site if the laboratories are not on site.</p> |
| Distribution Transport arrangements | <p>Describe how products are transported to either the purchasers or end users. If refrigerated systems are used it is important to specifically cover this area in detail.</p> |
| Third party Contracts | <p>Give names and addresses of any other organisation that provides or receives a service from your organisation together with a summary of the service provided e.g. analytical, manufacturing, packaging, maintenance of equipment etc.</p> |

Good Clinical Practice

“Good clinical practice is a set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects.”

In the UK, the GCP inspectorate is responsible for inspecting clinical trials for compliance with Good Clinical Practice.

Good Laboratory Practice

- Good Laboratory Practice (GLP) embodies a set of principles that provides a framework within which laboratory studies are planned, performed, monitored, recorded, reported and archived.
- These studies are undertaken to generate data by which the hazards and risks to users, consumers and third parties, including the environment, can be assessed for pharmaceuticals, agrochemicals, veterinary medicines, industrial chemicals, cosmetics, food and feed additives and biocides.
- GLP helps assure regulatory authorities that the data submitted are a true reflection of the results obtained during the study and can therefore be relied upon when making risk/safety assessments.

How MHRA monitor the safety of medicines

1) Pharmacovigilance

Pharmacovigilance is the process of:

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

Information sources used for pharmacovigilance

1. spontaneous adverse drug reaction (ADR) reporting schemes, for example, the Yellow Card Scheme
 2. clinical and epidemiological studies
 3. worldwide published medical literature
 4. pharmaceutical companies
 5. worldwide regulatory authorities
 6. morbidity and mortality databases.
- Information from all of these sources is carefully screened and may identify unexpected side effects; 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 of the medicine, such as:
 1. restrictions in use
 2. changes in the specified dose of the medicine
 3. introduction of specific warnings of side-effects in the product information.

2) Yellow Card Scheme

- The MHRA and the Commission on Human Medicines (CHM) run the UK's spontaneous adverse drug reaction (ADR) reporting scheme - called the Yellow Card Scheme. This receives reports of suspected adverse drug reactions (ADRs) or side effects from healthcare professionals and patients
- The Yellow Card Scheme is the main ADR reporting scheme in the UK and was introduced in 1964 after the thalidomide tragedy highlighted the urgent need for routine monitoring of medicines.
- The Yellow Card scheme is administered by the MHRA with the support of five Yellow Card Centres:
 1. Yellow Card Centre Mersey.

2. Yellow Card Centre Wales.
3. Yellow Card Centre Scotland.
4. Yellow Card Centre Northern and Yorkshire.
5. Yellow Card Centre West Midlands.

How is Yellow Card data used to improve patient safety?

- Information gathered from Yellow Card reports from patients and healthcare professionals is continually assessed by a team of safety experts comprising of doctors, pharmacists and scientists who study the benefits and risks of medicines
- From the data collected on Yellow Card reports the following can result:
 1. Patient information leaflets (PILs) and Summaries of Product Characteristics (SPCs) for medicines are updated when new safety issues are identified.
 2. Letters are sent to all doctors and pharmacists by post or electronic cascade to provide urgent warnings about drug hazards.
 3. Safety information is published in drug safety bulletin, '[Drug Safety Update](#)'. This is produced monthly by the MHRA and CHM.
 4. Fact sheets are produced for major safety issues for both healthcare professionals and patients
 5. Safety alerts are published on website
 6. Listings of suspected ADRs to drugs, Drug Analysis Prints (DAPs)
 7. On rare occasions, the withdrawal of a medicine if there is a risk to public health.

3) New drugs and vaccines under intensive surveillance

What are Black Triangle drugs (▼)?

The Commission on Human Medicines (CHM) and the MHRA encourages the reporting of all suspected reactions to newer drugs and vaccines, which are denoted by an inverted Black Triangle symbol (▼). This symbol appears next to the name of a relevant product:

1. the British National Formulary (BNF)
2. in the British National Formulary for Children (BNFC)
3. in the Nurse Prescribers' Formulary (NPF)
4. in Monthly Index of Medical Specialities (MIMS)
5. in the Association of the British Pharmaceutical Industry (ABPI) Medicines Compendium
6. on advertising material
7. in [Drug Safety Update](#)

Why is it a Black Triangle product (▼)?

- A Black Triangle is assigned to a product if the drug is an active substance which has been newly licensed for use in the UK.
- However, a product containing previously licensed active substances may also be monitored and assigned Black Triangle status if it meets one or more of the following criteria:
 1. it contains a new combination of active substances
 2. administration of the drug via a new route of administration or drug delivery system
 3. a significant new indication which may alter the established risk/benefit profile of that drug
 4. an established medicine which is to be used in a new patient population.
- All similar biological medicines (biosimilars) have a Black Triangle symbol because every new biological product has been developed to be similar to an

existing biological product, however may not have an identical structure therefore requires intensive monitoring for safety and efficacy.

Why do MHRA monitor Black Triangle drugs (▼)?

It receives all reports of suspected adverse reactions associated with Black Triangle products, in order to:

- confirm risk/benefit profiles established during the pre-marketing phase
- increase our understanding of the safety profiles of new medicines
- ensure that we identify previously unrecognised side effects as quickly as possible.

Why is there an asterisk next to the Black Triangle (▼*)?

Some established products may have the Black Triangle symbol reinstated - for instance if the product has been approved for use in a significantly new indication or in a new population. These products are denoted by an asterisk next to the Black Triangle (▼*).

How long is a drug under the Black Triangle Scheme (▼)?

The MHRA assesses the Black Triangle status of a product usually two years after marketing. However, there is no standard time for a product to retain Black Triangle status. The symbol is not removed until the safety of the drug is well established.

4) Defective Medicines Report Centre

- The MHRA's Defective Medicines Report Centre (DMRC) plays a major part in the protection of public health by minimising the hazard to patients arising from the distribution of defective medicinal products by providing an emergency assessment and communications system between suppliers of medicinal products, the regulatory authorities and the users.
- It achieves this by receiving and assessing reports of suspected defective medicines, monitoring and as necessary advising and directing appropriate actions by the responsible authorisation holder and communicating the details of this action as necessary and with appropriate urgency to recipients of the products and other interested parties in the UK and elsewhere by means of drug alerts.

Recalls and drug alerts

- Drug alerts are classed from I to IV according to their criticality and the speed with which action must be taken to remove the defective medicine from the distribution chain and, where necessary, from the point of dispensing and use.
- This varies from immediate action for a Class I alert, to action within five days for a Class III alert. In some low-risk circumstances the product may be allowed to remain in the supply chain when the DMRC will issue a Class IV "caution in use" alert.

5) Drug Analysis Prints (DAPs)

DAPs contain complete listings of all suspected adverse drug reactions or side effects, which have been reported by healthcare professionals and patients to the MHRA, via the Yellow Card Scheme.

How MHRA regulates device?

Medical device agency (MDA):

Medical device agency regulates medical device (instruments, apparatus, appliances, material and software used alone or in the combination to prevent, diagnose, treat disease or alter pharmacological action of the body).

Aim:

- Take all reasonable steps to protect the public health ensuring medical devices and equipment meet appropriate standards, safety, quality and performance in European Union.
- Toiletry and cosmetics products, personal protective equipment are not included in medical device.
- History: Established as a part of NHS in 1948 and changed to Agency status in 1994.

Activity areas:

1. Clinical (Medical and Nursing)
2. Device Technology and Safety
3. Device Evaluation Service
4. European and Regulatory Affairs (ERA)

The Agency - through ERA - represents the UK on all regulatory matters affecting medical devices.

The Three Directives

1) Active Implantable Medical Devices Directive(90/385/EEC)

Examples of AIMDs include: implantable cardiac pacemakers, implantable defibrillators, Leads, electrodes, implantable nerve stimulators, bladder stimulators, sphincter stimulators, diaphragm stimulators, cochlear implants, implantable active drug administration device, catheters, sensors for implantable active monitoring devices, Programmers, software, transmitters.

2) Medical Devices Directive

Directive 93/42/EEC covers the placing on the market and putting into service of Medical Devices.

3) In Vitro Diagnostic Medical Devices Directive

Directive 98/79/EC cover devices used in vitro for the examination of a specimen derived from the human body, including reagents, instruments and specimen receptacles.

The main purpose of the Directive is to

- Harmonise national controls, so allowing free movement of medical devices throughout the European Union and EFTA whilst at the same time ensuring that all devices within the Union are reasonably safe in use.
- specifies “essential requirements” which must be met before any device can be placed on the market;
- introduces controls covering the safety, performance, specification, design, manufacture and packaging of devices;
- specifies requirements for assessment of clinical investigation protocols, and the evaluation of any adverse incidents that occur

- introduces a system of assessment of clinical investigation protocols, which is matched to the degree of risk inherent in the device
- Empowers a Competent Authority to identify and designate “notified bodies” who check and verify that devices meet the relevant essential requirements.

Clinical investigation in the UK: requirements of the regulations

1. In order to be able to CE mark any device, a manufacturer must demonstrate that the stated device complies with the relevant Essential Requirements. To demonstrate such compliance, it will usually be necessary to provide clinical data. Clinical data can consists of:
 - 1) Critical evaluation of the relevant scientific literature
 - 2) Critical evaluation of the results of all the clinical investigations made
- **Clinical investigation** is any systematic investigation or study in human subjects, undertaken to verify the safety and performance of a device, under normal conditions of use.
2. Such an investigation must be designed to determine any undesirable side effects under normal conditions of use and assess whether these constitute risks when weighed against the intended performance of the device.

A clinical investigation of a non-CE-marked medical device should at least be considered in the following circumstances:

1. The device is an implantable or Class III medical device
 2. The introduction of a completely new concept of device into clinical practice where components, features and/or methods of action, are previously unknown;
 3. where an existing device is modified in such a way that it contains a novel feature particularly if such a feature has an important physiological effect; or where the modification might significantly affect the clinical performance and/or safety of the device;
 4. where a device incorporates materials previously untested in humans, coming into contact with the human body or where existing materials are applied to a new location in the human body or where the materials are to be used for a significantly longer time than previously, in which case compatibility and biological safety will need to be considered;
 5. Where a device, either CE-marked or non-CE-marked, is proposed for a new purpose or function;
 6. Where in vitro and/or animal testing of the device cannot mimic the clinical situation;
 7. Where there is a new manufacturer especially of a high-risk device.
- Before devices intended for clinical investigation in the UK, the manufacturer of the device must give 60 days prior notice to the Secretary of State for Health by writing to the UK Competent Authority. If, within 60 days of formal acceptance of the Notice, the UK Competent Authority has not given written notice of objection, the clinical investigation may proceed.
 - In particular the clinical investigation must:
 1. • be performed on a basis of an appropriate plan with well-defined aims and objectives;
 2. • be performed in circumstances similar to the intended conditions of use;
 3. • include sufficient devices to reflect the aims of the investigation taking into account the potential risk of the device;

4. • examine appropriate features involving safety and performance and their effects on patients so that the risk/benefit balance can be satisfactorily addressed;
5. • Fully record all adverse events and report serious adverse events to the UK Competent Authority;
6. • be performed under the responsibility of a medical practitioner or a number of medical practitioners; and
7. • include the making of a final written report, signed by the medical investigator(s) responsible, which must contain a critical evaluation of all the data collected during the clinical investigation, with appropriate conclusions.

Documentation required for all submissions

- 1) General Information
- 2) Details allowing device to be identified
- 3) Other device details
- 4) Detailed information on the device
- 5) Clinical investigation plan: Means a document that includes detailed information on the rationale, aims and objectives, design and proposed analyses, methodology, and conduct of the clinical investigation.

CLASS I devices

- Medical Devices Directive, 93/42/EEC, require all medical devices to carry the CE marking unless they come within the definitions of custom-made devices or devices intended for clinical investigation.

Examples

1. Administration

- A 1 Measuring and mixing devices for medicines
- A 2 Inhalation Devices (e.g. Chamber Spacers)
- A 3 Sets - Solution/Irrigation (Gravity Only)
- A 4 Syringes (Hypodermic/Oral/Irrigation)

2. Dental

- B 3 Dental Instruments (Reusable and Non-Powered)
- B 4 Dental Prophylaxis Paste (Non-Fluoride)
- B 7 Orthodontic Materials (Extra-Oral/Intra-Oral Transient and Short-Term Use)
- B 11 Dental Unit Accessories
- B 12 Artificial Teeth
- B 13 Base Materials
- B 14 Dental Mouth Wash Tablets (Non-Medicated)
- B 15 Denture Lining Materials/Adhesives
- Z 169 Denture Cleaning Liquids/Tablets (Non-Disinfecting) (Dental Devices)

3. Diagnostic

- C 1 Conductive Gel
- C 2 Electrodes/Transducers and Accessories
- C 4 Sphygmomanometers and Accessories
- C 5 Stethoscopes
- C 6 Thermometers (Clinical)
- C 8 Blood Sampling Devices (Re-Usable)
- C 9 Endoscopes/Endoscopic Instruments and Accessories
- C 11 Laryngoscopes/Otoscopes and Accessories

- C 12 X-Ray Cassettes, Cassette Holders, Image Enhancers and Intensifying Screens
- C 13 Radiographic Film Processing Chemicals
- C 15 Sampling and Cell Collection Devices (Patient Contact - not IVDs)

4. Dressings

- D 1 Bandages (e.g. Support/Tubular/Adhesive/Plaster of Paris/Cast Liners/Resin)
- D 2 Cotton Wool/Gauze/Non Woven (Ribbons/Swab/Buds)
- D 3 Adhesive Plasters/Dressings/Tapes/Barrier Films
- D 4 Eye Occlusion Plasters/Shields and Corneal Shields
- Z 149 Dressing Adhesive Removers (Single Use)

5. Ophthalmic

- F 2 Fundas Cameras/Keratometers/Slit Lamp Microscopes and Associated Software
- F 3 Low Vision Aids
- F 5 Ophthalmoscopes/ Retinascopes
- F 6 Spectacle Lenses
- F 7 Spectacle Frames
- F 8 Ready-Made Spectacles (Non-Prescribed)
- F 9 Sight Testing Devices
- O 9 Schirmer Tear Test (Sterile Product) (Ophthalmic and Optical Devices)
- Z 45 Class I Tonometer (Reusable)
- Z130 Contact Lens accessories (Ophthalmic and Optical Devices)

6. Surgical

- H 1 Umbilical Clamps/Tape
- H 2 Tubes (Oesophageal/Rectal) and Accessories
- H 3 Enema and Douche Devices
- H 4 Incision Drapes/Theatre Clothing
- H 5 Surgical Instruments (Reusable and Non-Powered)
- H 7 Airway Devices/Monitoring Equipment and Accessories
- H 8 Non-Invasive Drainage Devices and Accessories
- H 10 Sterilisation Packaging
- H 11 Accessories for Implantable Devices (Non-Invasive)
- Z 136 Electrosurgical Accessories (e.g. Transient Invasive Electrodes, Footswitches) (Electro-Medical Mechanical Devices)

7. Equipment and Furnishings

- Z 135 Autoclave Accessories (e.g. Trays and Tray Lifters, Shelves, Racks) (Hospital Hardware)

8. Orthoses and Prostheses

- 9. Walking Aids and Wheelchairs**
- 10. Waste Collection**

11. Other

- Z 48 Telemedicine Accessories (Reusable)
- Z 129 Acupressure Devices

Essential requirements of Class I devices:

- 1) Review the classification rules to confirm that their products fall within Class I (Annex IX of the Directive)
- 2) Technical documentation:

| Technical Requirements | documentation | Guidance |
|---|---------------|--|
| General description of the product | | name, model number and size |
| Raw material and component documentation | | details of raw materials, drawings of components and/or master patterns and any quality control procedures |
| Intermediate product and sub assembly documentation & final product documentation | | circuits, and formulation specification, relevant manufacturing methods |
| Packaging and documentation | labeling | copies of all labels and any instructions for use |
| Design verification | | results of qualifications tests and design calculations relevant to the intended use of the product |
| Compliance with essential requirements and harmonized standards | | sterilization, labeling and information, biocompatibility, electrical safety, risk analysis, product group standards |
| Risk analysis, clinical data records, Manufacturing and test records | | Generally not require a special clinical investigation |

- 3) “EC Declaration of Conformity” before applying the CE marking to their devices. The “EC declaration of conformity” is the procedure whereby the manufacturer or his authorised representative prepares the required technical documentation, puts into place corrective action and vigilance procedures and declares that the products meet the essential requirements set out in Annex I of the Directive.
- 4) notified body approval for sterility or metrology aspects of their devices, where applicable
- 5) post market surveillance, corrective action and vigilance procedure
- 6) registration with the Competent Authority
- 7) notify the Competent Authority, in advance, of any proposals to carry out a clinical investigation to demonstrate safety and performance of a device as required by the Regulations

Custom made devices

'Custom made' means that the product is manufactured specifically in accordance with a written prescription of a duly qualified medical practitioner or a professional user and it is intended for the sole use of a particular patient and are not adapted from mass produced items.

Examples

- K 1 Dental Appliances/Prostheses
- K 2 Hearing Aid Inserts
- K 3 Prescribed Orthopaedic Footwear
- K 4 Artificial Eyes
- K 5 Orthoses and Prostheses - External (Made Direct from Casts/Prescriptions)
- K 6 Orthopaedic Implants
- K 7 Maxillo-Facial Devices
- K 8 Standing and Walking Frames
- K 9 Ligament and Tendon Repair Implants
- K 10 Spectacle Frames

- Y 4 Mandibular Advancement Device (Anaesthetic and Respiratory Devices)
- Y 10 Insoles (Made Direct from Casts) (Technical Aids for Disabled Persons)
- Y 13 Postural Support Products (Technical Aids for Disabled Persons)
- Y 15 Splints (Limb/Body/Ear)/Collars (Single Use)

The essential requirements for custom made devices

The manufacturer should consider

1. chemical, physical and biological properties of the device
2. infection and microbial contamination
3. construction and environmental properties
4. protection against radiation
5. requirements for medical devices connected to or equipped with an energy source
6. information supplied by the manufacturer, including labels

As a minimum requirement the labels on a custom-made device must include

1. The name or trade name and address of the manufacturer or, for devices imported into the European Economic Area (EEA), the name and address of a representative based there;
2. The details strictly necessary for the healthcare professional to identify the device and the contents of the packaging (e.g. patient name/description of device);
3. The words “custom-made device”.

Recall notice

MHRA will only serve a recall notice, where it has reasonable ground for believing that a product is a dangerous product, which has already been supplied and/or made available to consumers.

Need for a recall:

- The hazard arising from the device shortcoming.
- Risk outweighs benefits of the device.

Recall Procedure:

- The return of a medical device to the supplier
- Device modification by the supplier at the site of installation
- Device exchange
- Device destruction
- Retrofit by purchaser of manufacturer's modification or design change

What triggers recall?

- Information depicting unacceptable increase in risk posed by a medical device.
- Post-marketing surveillance.

Notification of Recall:

- The manufacturer or authorized representative has to notify the CA of each EC member State in which the recall is being conducted.
- For Class I, II, III and IV D's listed in Annex II or those for self testing, manufacturer should notify additionally the CA of the country where their authorized representative reside.
- Notification should be made before and when the recall letter is being issued
- Where practical, MDA should be advised of the recall prior to its initiation

Information MDA needs from Manufacturer:

1) Details of the problem:

- Details of the factors giving rise to the recall, including summary of relevant adverse incidents
- Technical details of the device shortcoming if known
- Potential hazard presented by use of the device
- Circumstances under which the device is used and when the hazard may occur
- Indication of likelihood of hazard occurring
- Conclusions of tests and other investigations on suspect or other samples if available
- (draft) recall letter

2) Details of the product

- Whether device is CE-marked and device classification/category;
- Device model name/number and description;
- Batch or serial number(s) of affected devices;
- Manufacturer's contact details if reported by distributor;
- When affected products were distributed;
- UK customers of affected product;
- Names of other EEA countries affected by the recall
- The identity of the relevant Notified Body where applicable

Implementation of the recall:

To enable an effective recall manufacturers have a responsibility to:

- Implement an effective post-market surveillance
- Maintain product records
- Establish a recall procedure

Decontamination of Medical Devices:

The MAC (Microbiology Advisory Committee) Manual addresses aspects of the decontamination. This document is published by the Medical Devices Agency.

Part 1: describing the general PRINCIPLES of the processes that are available for decontamination (first published 1993).

Part 2: containing PROTOCOLS for decontamination using cleaning, disinfection and sterilization processes (published 1996).

Part 3: describing PROCEDURES for the decontamination of specific items of equipment, published in 2 Sections: Section 1 (1999) and Section 2 (2000).

PRINCIPLES

- The choice of decontamination method may be related to the infection risk associated with the intended use of the equipment

| Risk | Application of item | Recommendation |
|--------------|---|---|
| High | in close contact with a break in the skin or mucous membrane; Introduced into sterile body areas. | Sterilization. |
| Intermediate | in contact with mucous membranes; contaminated with particularly virulent or readily transmissible organisms; Prior to use on immunocompromised patients. | Sterilization or disinfection required. Cleaning may be acceptable in some agreed situations |

| | | |
|------------|---|------------------|
| Low | in contact with healthy skin; Not in contact with patient. | Cleaning. |
|------------|---|------------------|

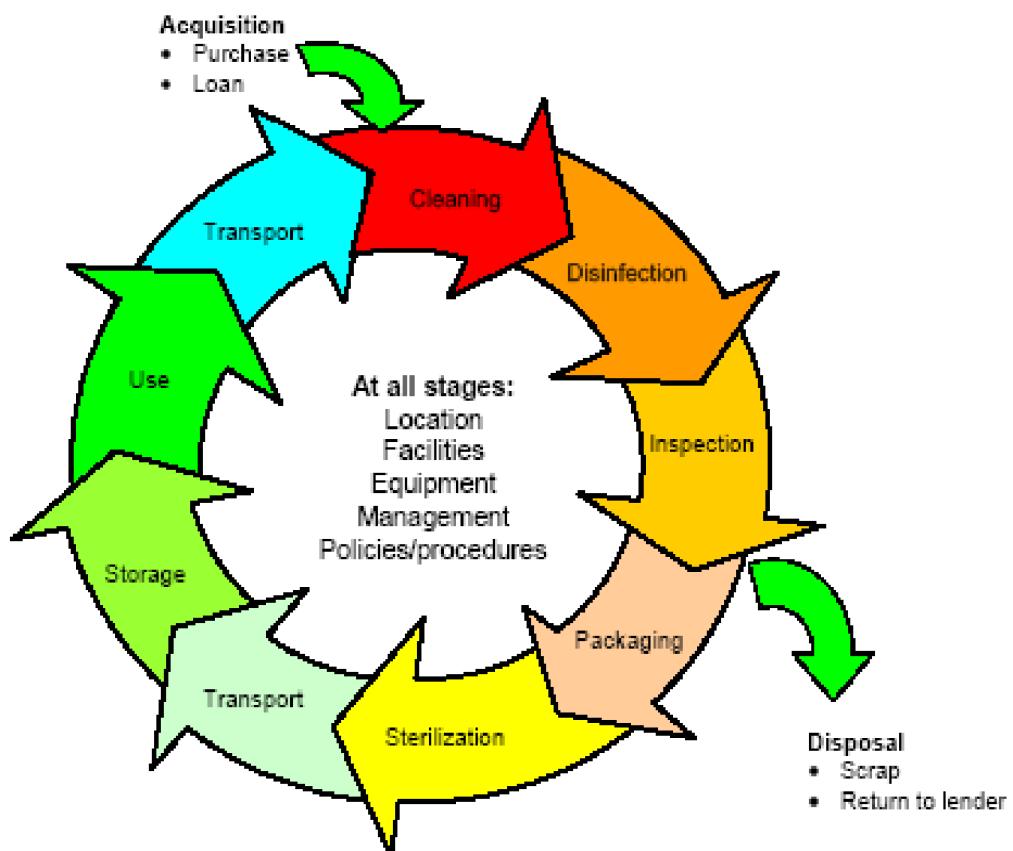
Classification of infection risk associated with the decontamination of medical devices

- The choice of decontamination method will also depend on many other factors including the manufacturer's instructions, the nature of the contamination, the time required for processing, the heat, pressure, moisture and chemical tolerance of the item or of individual components, the availability of the processing equipment and the quality and risks associated with the decontamination method, the physical nature of the equipment, e.g. size.

PROTOCOLS

Part 2 describe the protocols for rendering medical devices safe for subsequent handling or use. It provides protocols for both

- (1) The reprocessing of devices intended for clinical reuse and
- (2) The decontamination of devices prior to inspection, service or repair and/or that is the subject of complaint or investigation using the cleaning, disinfection and sterilization processes.



Work flow chart – decontamination life cycle

- Figure highlights each stage of the decontamination process through which surgical instruments pass before every use. At all stages of reprocessing, the following issues need to be taken into account:
 1. The location and activities where decontamination takes place
 2. Facilities and equipment at each location
 3. Ensuring that equipment used is validated, maintained and tested in accordance with manufacturer's guidelines and legislation

4. The existence of effective management arrangements
5. The existence of policies and procedures for all aspects of decontamination work.

PROCEDURES

Section 1 provides an overview of

- The European Directives for medical devices.
- Information provided by manufacturers
- Reprocessing
- **Cleaning instructions**
 1. Instructions on how to dismantle (and subsequently reassemble) the device, if necessary.
 2. Cleaning agents, in generic or brand-named terms, known to be effective and compatible with the device.
 3. Any accessories, where relevant, which may assist the cleaning process, such as automatic washers, ultrasonic cleaners or brushes.
- **Disinfection instructions**
Generic or brand-named disinfectants known to be effective and compatible with the device.
- **Method(s) of sterilization**
The name of the process (e.g. steam sterilization); the type of cycle (e.g. pre vacuum/porous load); and any relevant cycle parameters (e.g. 134-137°C for a minimum holding time of 3 minutes).
- Purchase of medical devices and equipment
- Standards

Section 2 Provides general procedures for the following groups of equipment:

- • Endoscopes and accessories
- • Dental equipment
- • Ophthalmic equipment
- • Surgical instruments
- • Ventilators
- • Miscellaneous items.

How MHRA regulate advanced therapy medicinal products

- An ATMP is a medicinal product which is either:
 1. a gene therapy medicinal product
 2. a somatic cell therapy medicinal product
 3. a tissue engineered product
- The ATMP Regulation came into force on 30 December 2007. The provisions of the Regulation applied from 30 December 2008. The UK's legislation for implementing the Regulation and the requirements that will apply under the hospital exemption scheme will be made and laid in Parliament later in 2010.
- Under the ATMP Regulation, the centralised authorisation procedure will apply to ATMPs which are intended to be placed on the market in the Community. A new committee, the committee for advanced therapies (CAT) has been established at the European Medicines Agency (EMA) s responsible for preparing a draft opinion on the quality safety and efficacy of each ATMP for which a marketing authorisation application is submitted.
- The CAT's opinion will be submitted to the EMA's Committee for Medicinal Products for Human Use (CHMP) for final approval.

- In the UK, the MHRA is the supervisory authority for UK manufacturers or importers of entrally authorised ATMPs, as well as the competent authority for
 1. ATMPs which are repared and used under the hospital exemption and made and upplied under the Specials' scheme.
 2. The assessment of applications for clinical trial authorisations and the associated manufacturer's licence for investigational ATMPs.

Reference:

www.mhra.gov.uk