

Making Regulatory Decisions about Medicines and Medical Devices

Revised in September 2007

This document sets out:

- the main regulatory decisions that are made about medicines and medical devices (page 2),
- the principles that inform these decisions (page 3),
- the questions that are considered to ensure that the decisions are reasonable (page 4), and
- who makes decisions about medicines and medical devices – which includes bodies other than MHRA (page 5).

The Medicines and Healthcare products Regulatory Agency (MHRA) has drafted this document after consultation with a range of external stakeholders, including healthcare professionals, bodies which represent patients and the public, and the pharmaceutical and medical devices industries. An earlier version was put on the MHRA website with an invitation for comments.

We do not see this document as the last word on the subject and may undertake further consultation.

To summarise the role of the MHRA:

- We are the government agency responsible for ensuring that medicines and medical devices work, and are acceptably safe.
- No product is risk-free. Underpinning all our work lie robust and fact-based judgements to ensure that the benefits to patients and the public justify the risks.
- We keep watch over medicines and devices, and we take any necessary action to protect the public promptly if there is a problem.
- We aim to make as much information as possible publicly available.
- We enable greater access to products, and the timely introduction of innovative treatments and technologies that benefit patients and the public.
- We encourage everyone – the public and healthcare professionals as well as the industry – to tell us about any problems with a medicine or medical device, so that we can investigate and take any necessary action.

The term “medicines” embraces both pharmaceutical and biological medicines, and vaccines.

The term “medical devices” includes medical equipment. Medical devices are all products, except medicines, used in healthcare for the diagnosis, prevention, monitoring or treatment of illness or disability. Examples include X-ray and other imaging equipment, pacemakers, artificial joints, anaesthetic equipment, pregnancy test kits, infusion equipment, beds, wheelchairs, condoms and surgical dressings.

This document refers to both kinds of products however they are available, whether by prescription or over the counter, or in use by healthcare professionals for the benefit of their patients.

It is important to note that these few pages do not attempt to provide a detailed explanation of MHRA’s legal framework and its regulatory processes. Much more about these can be found on the Agency’s website – www.mhra.gov.uk/. There are also some significant differences between the ways medicines and medical devices are regulated. While the document refers to some of them, its main purpose is to cover the issues common to both kinds of product.

A. What kinds of decisions are made about medicines and medical devices?

The Agency operates a range of regulatory systems which aim to ensure that:

- 1 The design and conduct of clinical trials for medicines and medical devices provide acceptable levels of protection for participants.
- 2 A new medicine or medical device is allowed on to the market with a licence or CE-mark only if there is enough evidence that the potential benefits will outweigh the likely risks.

CE marking for a device is a claim of compliance with the Essential Requirements of European Directives. It has a similar function to that of a licence – or market authorisation – for a medicine. The two kinds of authorisation are intended to provide assurance that a product's safety has been assessed before marketing, together with its efficacy (for medicines) or performance (for devices).

- 3 We receive enough reliable information from healthcare professionals, patients and the public, and companies, about adverse events with medicines and devices that are in use.
- 4 If new information becomes available about a product's benefits and/or risks, or about the quality of manufacture or supply, it will, if appropriate, be withdrawn or have its use restricted.
- 5 If there is new information about an adverse effect of a product that needs communicating to healthcare professionals or the public, we or companies issue advice or warnings with an appropriate degree of urgency and through appropriate channels.
- 6 Good advice is given to professionals or the public if we become aware that a medicine or medical device is inappropriately or incorrectly used, or is inadequately maintained, sterilised or tested.
- 7 The availability of a medicine accords with the risks it poses. It could be available for purchase from any shop, available only under the supervision of a pharmacist, or available only with a prescription.
- 8 The public can have confidence that CE-marked medical devices available over the counter can be used at home without having to be in the hands of a healthcare professional.
- 9 The supporting information for professionals and the public about a medicine or medical device is appropriate, readable and fit for purpose.
- 10 Advertising or marketing claims for medicines are justified and targeted at appropriate audiences.
- 11 Pharmaceutical companies and device manufacturers meet their legal obligations in respect of medicines and medical devices.
- 12 The supply of unauthorised or counterfeit medicines and medical devices is prevented or at least disrupted, and inappropriate sales of second-hand devices are discouraged.
- 13 Information in relation to our decisions is made available unless it cannot for legal or other reasons be made public, striking a balance between the need for openness and the need to respect commercially sensitive information.

B. What principles inform the decisions?

- 1 Medicines and medical devices bring widespread benefits for patients and the public but no product is free of risk. Many decisions involve weighing risks of harm against the likelihood of benefits. If a product is available for use, its risks must be acceptable in relation to the potential benefits to patients and users.
- 2 Some risks are known when a product goes on the market but others will only become known later when it is widely used, especially if adverse events are rare.
- 3 Decisions will be based on good science and robust methodology. Judgements on safety, quality and performance will be informed by all available, relevant and reliable evidence, with the burden of proof often resting on companies.
- 4 A cautious approach to a decision will be needed where there is scientific uncertainty about the existence or extent of a risk but reasonable grounds for anticipating the possibility of severe adverse effects.
- 5 The Agency is concerned about the safety, quality, performance and use of a medicine or device throughout its life. The Agency will continue to seek and require additional information on risk and benefit, particularly since the initial authorisation or compliance with requirements may have been based on limited information. If the relationship between risk and benefit changes, so may the approval or classification of the product, or the advice to prescribers and users
- 6 The Agency is committed to the principles of equality, and will not improperly or arbitrarily discriminate, for example on the basis of age, sex or race. However, the initial and ongoing approval of a product will legitimately take account of factors such as age, sex or race, particularly if any of these populations is a specific target for benefits or poses specific risks. So, for example, the effects of a product on children, on the elderly or in pregnancy may require explicit consideration
- 7 The financial cost of a product does not enter into the Agency's decision-making processes, though bodies such as NICE and the NHS are concerned with costs

There is widespread confusion between the roles of MHRA and NICE (the National Institute for Health and Clinical Excellence). MHRA is concerned about the relationships between benefits and risks; NICE is concerned, inter alia, about the relationships between benefits and costs. As a considerable over-simplification, MHRA says a product can be sold while NICE says it can be bought (by the NHS).

- 8 The Agency's decisions will as far as possible take account of the known views of relevant stakeholders such as medical specialists and patient representative groups
- 9 Decisions are made within processes which comply with legal obligations and in which the public can have confidence
- 10 The Agency's decisions will as far as possible be transparent and open to public scrutiny; a reasonable person reviewing our decision should understand the rationale
- 11 If the Agency withholds information because of legal obligations such as the requirement to protect confidentiality, it will give its reasons for doing so.
- 12 The staff of the Agency and the members of its Advisory Committees are not influenced in their decisions by financial or other interests in the industries concerned.

C. What questions should be considered to ensure that reasonable decisions are made?

We do not expect that all these questions will be considered in all situations or that there will be simple yes or no answers to many of them. The list is not exhaustive, and other questions may be relevant in particular situations.

- 1 Does the product work and offer useful clinical benefit if used in its specified way?
Is there robust evidence that the product will do what the company says it will do?
- 2 What impact will the product have, or is it having, on both the quality and length of life in those patients who are treated with it or on whose behalf it is used?
- 3 Has the manufacturer demonstrated that it can consistently and reliably make the product to the required level of quality?
- 4 Does the evidence available before a product is marketed give a clear indication of all adverse effects that have been discovered, the likelihood that they will occur and their severity?
Have companies done all they reasonably can to identify, reduce and communicate risks?
- 5 If the available evidence on safety, quality or performance is uncertain or unclear, is more needed before a decision can be made?
- 6 Is there relevant evidence about everyday use of this or similar products, or do we need to seek such evidence?
A scientifically excellent clinical trial is of limited value if its design does not reflect the likely use of the product in everyday situations
- 7 From knowledge of how the product works, is it possible to predict other adverse effects that may occur when the product is used with larger and wider groups of people, or in conjunction with other products? If so, are there clear plans in place to track and manage the risks?
- 8 Can the risk of adverse effects be limited by restricting the product's use to specific groups of patients, or to particular dosages or durations of use?
- 9 What risks are associated with the condition the product is designed to manage?
Do the risks of not treating the condition outweigh the risks associated with the product? Is it a very serious/debilitating condition, or a mild and self-limiting one? Greater risks may be acceptable for products that markedly reduce suffering or treat life-threatening conditions, especially those for which no other effective treatment is available
- 10 Can the Agency accept less evidence on which to base its decision if the rarity of the clinical condition means that more detailed evidence cannot reasonably be gathered?
- 11 Is the Agency prepared to accept early and limited evidence on which to come to a decision if a product, while appearing to have acceptable risks, offers significant or urgent benefits to public health or outstanding benefits to patients?
- 12 Are there, or can there be, warnings for the public as well as for healthcare professionals about the nature and likelihood of adverse effects, warnings that are understandable and specific enough for them to make informed choices or to restrict the usage?
If not, how else might the risks be managed? Would it be better not to allow the product to come onto or to remain on the market, or to restrict its availability?
- 13 Does the Agency's decision take account of the known views of the public about the balance between risks and benefits? If the public's views are in conflict with robust and comprehensive scientific evidence, should they carry any weight?
- 14 Does the Agency need to seek further views from relevant parties?
In addition to the scientific evidence, do we need views from healthcare professionals, organisations concerned with specific conditions, and/or patients who have used the product?

D. Who makes the decisions?

There are three main groups within the MHRA involved in regulatory decisions:

- Staff – the Agency’s professional staff make many decisions about the safety and performance of medicines and medical devices on a day-to-day basis, and about the quality of manufacturing and distribution. An Executive Board of senior staff oversees the work of the Agency and takes ultimate responsibility for the decisions made.
- Advisory Committees – groups of independent experts and lay representatives who advise on whether medicines and devices work and are acceptably safe, based on an evaluation of all relevant evidence, including that from the Agency. These groups include the Commission on Human Medicines, its Expert Advisory Groups, and the Committee on the Safety of Devices.
- The Agency Board – which is made up largely of external members, acts in a supervisory and advisory capacity and has a particular role in assuring the quality of decision-making.

In law, decisions by the Agency are decisions of the Secretary of State for Health who is accountable to Parliament. Ministers also make decisions on matters of significant public concern from time to time, advised by the Agency or its expert committees.

There are other organisations and bodies outside MHRA which are also concerned with safety, quality and/or performance, principally in that:

- Organisations called Notified Bodies carry out a compliance assessment before manufacturers can place certain medical devices¹ on the market. Notified Bodies in the UK are designated and audited by MHRA.
- Many decisions made by or within other Member States of the European Union and by the European Medicines Agency² must be respected or taken into account within the UK, just as decisions of MHRA can have an impact on other Member States. Experiences of problems are also shared in both directions.
- Clinical trials of products are subject to the approval of ethics committees, complementing the role of MHRA, which is principally concerned with the scientific evidence.

We do not and should not have direct influence over ethics committees or European partners but recognise that their decision-making often follows similar principles; if we have cause for concern about decisions taken by others, we make that known through appropriate channels.

It is for doctors and other healthcare professionals to determine the suitability of particular medicines or medical devices for individual patients under their care, weighing benefits against risks and subject to guidance from the NHS and NICE.

Patients and the public will often have their own views about the suitability of particular medicines or medical devices. They are usually free to decide for themselves whether to use the products or not, supported by reliable information about risks and benefits.

We encourage both patients and healthcare professionals to report adverse events, through the [Yellow Card](#) scheme for medicines or [Adverse Incident report forms](#) for devices. These reports are important to the Agency, which analyses them alongside other new sources of information to determine whether action is needed.

¹ This applies to medium and high risk devices, including active implantable devices and certain in-vitro diagnostic devices, and devices supplied sterile or which have a measuring function. Assessment may include quality assurance, examination of the design or product testing. For other lower risk devices, manufacturers make declarations that their devices meet statutory requirements for CE-marking.

² The EMEA must authorise medicinal products derived from biotechnology and other high-technology processes, and medicines for certain diseases. The evaluation of evidence is delegated to regulatory agencies of Member States, including MHRA, but the concerns of all Member States are taken into account.