

MLX 287

CONSULTATION LETTER ON THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2003

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LIST OF ABBREVIATIONS

ABPI Association of the British Pharmaceutical Industry

AHPPI Association of Human Pharmacologists in the Pharmaceutical

Industry

CPMP Committee on Proprietary Medicinal Products

CSM Committee on Safety of Medicines

CTA Clinical Trial Authorisation
CTC Clinical Trial Certificate

CTMP Clinical Trial of a Marketed Product

CTX Clinical Trials Exemptions
DDX Doctors and Dentists Exemption
EEA European Economic Area

EEC European Economic Community

EMEA European Medicines Evaluation Agency

EU European Union

GCP Good Clinical Practice

GMP Good Manufacturing Practice HVT Healthy Volunteer Trials

ICH International Conference on Harmonisation

LA Licensing Authority

LREC Local Research Ethics Committee

MA Marketing Authorisation MCA Medicines Control Agency

MHRA Medicines and Healthcare products Regulatory Agency

MREC Multicentre Research Ethics Committee

OP Oualified Person

RIA Regulatory Impact Assessment

S.I. Statutory Instrument

SPC Summary of Product Characteristics SUSAR Serious Unexpected Adverse Reaction

UKECA United Kingdom Ethics Committee Authority

EU DIRECTIVE 2001/20/EC ON GOOD CLINICAL PRACTICE IN CLINICAL TRIALS – CONSULTATION ON IMPLEMENTING REGULATIONS

1 Purpose of consultation

The Clinical Trials Directive heralds certain additional responsibilities for the Medicines Control Agency (MCA), for ethics committees and for those running or supporting clinical trials of medicines for human use, including the NHS and those funding trials.

The Secretary of State for Health is proposing to implement the legislative requirements of the Directive by means of Regulations under section 2(2) of the European Communities Act 1972. This consultation document seeks your views and comments on the proposals for implementation and on the draft implementing Regulations.

The implementing Regulations would apply to the whole of the United Kingdom, as is the case with existing legislation relating to medicines control. The consultation document is therefore being circulated to a wide range of individuals, companies and organisations throughout the UK.

Guidance from the European Commission about the requirements of the Directive was issued for consultation on 12 July 2002 and the consultation period closed on 2 October 2002. Final Commission regulatory guidelines to accompany the Directive are expected to be available during the consultation period; the latest available drafts are available on the EU Commission website "www.pharmacos/eudra.org".

The Medicines Control Agency, an executive agency of the Department of Health, is responsible for medicines control and is leading this consultation exercise. As consultees may be aware, from 1 April 2003 the MCA will become the Medicines and Healthcare products Regulatory Agency (MHRA). In this document references to the MCA from the 1 April 2003 can be read as reference to the MHRA. Please send your replies to:

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2 Background

The full title of the Directive is Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, Regulations and administrative

provisions of the Member States relating to implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

Agreement on the Directive was reached in February 2001 and the final version was published in the *Official Journal of the European Communities*¹ on 1 May 2001 and is also available on the Commission's website, which is

http://www.europa.eu.int/eur-lex/en/search/search_lif.html. Member States have to prepare national provisions for complying with the Directive and must bring these provisions into force by 1 May 2004.

At present clinical trials are not directly regulated under the Community code relating to medicinal products for human use (see Directive 2001/83/EC) but are subject to UK national legislation. Directive 2001/83/EC does however require that applications for authorisation to place a medicinal product on the market in the Community should be accompanied by a dossier containing particulars and documents relating to the results of the clinical trials carried out on that product. Part 4 of Annex 1 to that Directive lays down uniform rules on the clinical trial documentation which must be submitted, including a requirement that all phases of clinical investigation should be designed, implemented and reported in accordance with good clinical practice. This has been supplemented by Community guidance on good clinical, practice, Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95).

Aside from these provisions, however, the current practices of Member States of the European Community diverge considerably on the rules as to the commencement and conduct of clinical trials; and the requirements for carrying them out vary widely across the Community. The primary purpose of the Directive on clinical trials is to simplify and harmonise the administrative provisions governing clinical trials by establishing a clear, transparent procedure, creating conditions conducive to an effective co-ordination of such clinical trials in the Community by the authorities concerned. This would facilitate the internal market in medicinal products while at the same time maintaining appropriate levels of protection for public health.

Many of the procedures and criteria set out in the Directive are already part of current UK clinical trials practice. However, the Directive lays down significant new controls which would affect all clinical trials of medicinal products in the UK.

The Directive requires that before a clinical trial may commence, an application must be submitted to the competent authority and authorised (in the United Kingdom this would be the licensing authority (LA) under the Medicines Act 1968, acting through the MCA) and obtain a favourable ethics committee opinion. Other new procedures relate to authorisation for the manufacture and import of medicinal products to be used in clinical trials, and ensuring that the principles of good clinical practice are complied with in the conduct of such trials.

The Regulations would make appropriate amendments to the Medicines Act, in order to transpose the provisions of the Directive; in particular repealing or amending the sections of the Act relating to clinical trials (see Schedule 9). In addition certain other

¹ OJ No L121, 1st May 2001, p.34

provisions of the Act would be applied to the new arrangements; see regulation 46 and Schedule 7. These draft provisions take account of other existing policy; for example, although section 118 of the Act (restrictions on disclosure of information) is applied, ethics committees would still publish their reports (regulation 14(10)).

The order of paragraphs in this document generally follows the order of the Articles in the Directive. Section 3 provides an overview of the proposed changes to the current legislation relating to clinical trials. Section 4 defines the scope and some interpreting definitions. Section 5 discusses details of the Regulations. Section 6 consults on the fees proposed to cover MCA's costs of assessment related to the Directive and discuss them. Section 7 describes the proposed transitional arrangements. Finally, Section 8 invites comments on the proposed Regulations, the proposed fees and the regulatory impact assessment that is attached at Annex C.

Transposition of the Directive's requirements into national legislation would be informed by the European Commission's guidance. The consultation period on the Commission's guidelines closed on 2 October 2002. The present position given in that Commission guidance is reflected in the consultation version of the Regulations. This guidance would not change any requirements in the Directive, but may provide additional interpretation on applying particular provisions in the Directive. It is expected that one part of this guidance which relates to good clinical practice would itself form an additional Directive (see section 3.1.4). Other areas which may be affected are indicated at appropriate points in the rest of this document.

3 Overview of the changes to the current legislation

3.1.1 Change to regulatory approach

While the current UK legislation regulates the supply of medicines for a clinical trial, the new Regulations would regulate the commencement and conduct of a clinical trial, and the manufacture of any medicinal products to be used in the trial (including reference products and placebos). Such products are referred to in the Regulations as "investigational medicinal products" (IMP). The Directive and Regulations would cover all clinical trials of medicinal products, including non-commercial trials (i.e. trials which are not directly supported by pharmaceutical companies) and Phase I healthy volunteer studies. "Non-interventional trials" are however excluded from the scope of the Directive and the Regulations – for the definition of non-interventional trials see regulation 2(1) of the draft Regulations and paragraph 4.1.5 below.

3.1.2 Current legislation

The current system of regulation under the Medicines Act 1968 requires that anyone who wishes to supply a medicinal product for a clinical trial, or to procure the supply of such product, must obtain a clinical trial certificate (CTC) – see section 31 of the Act. The legislation, however, provides for various exemptions from the requirement to hold a CTC (see sections 15, 31(5) and 35(8)(a)). Most trials in the UK are conducted under one or other of these exemption schemes. Transposing the Directive requires replacement of these schemes.

3.1.3 Current exemptions and certificates

Doctors and Dentists Exemption: A doctor or dentist conducting a clinical trial on his or her own patients and not on behalf of a commercial organisation or other third party, is exempt from the requirement to have a CTC (see section 31(5)), although they should notify the MCA under its Doctors and Dentists Exemption (DDX) scheme in accordance with the Medicines (Exemption from Licences)(Special Cases and Miscellaneous Provisions) Order 1972 (S.I. 1972/1200).

Clinical Trials Exemption: Any person other than an independent doctor or dentist that wishes to conduct a trial may obtain an exemption by applying for a Clinical Trials Exemption (CTX) in accordance with the Medicines (Exemption from Licenses) (Clinical Trials) Order 1995 (S.I. 1995/2808) and the Medicines (Exemptions from Licenses and Certificates) (Clinical Trials) Order 1995 (S.I. 1995/2809). This requires them to submit summaries of the supporting data normally required for a CTC.

Clinical Trials of a Marketed Product: Anyone wishing to conduct a trial with a licensed product may obtain an exemption by notifying the MCA in accordance with the (Medicines Exemption from Licences)(Clinical Trials) Order S.I. 1974/498.

Clinical Trials Certificate: The above exemptions can be obtained for most clinical trials conducted in the UK except those that pose an unusually difficult risk to benefit decision. Such trials require a CTC and before a decision is made on an application, the MCA refers the trial to the Committee on Safety of Medicines for advice on safety and on whether or not to grant a CTC.

3.1.4 Change to good clinical practice standards

In addition to the proposed new commencement procedures, the draft Regulations would provide that all clinical trials of medicinal products must be conducted in accordance with the conditions and principles of good clinical practice (GCP). Those conditions and principles would consist of both the principles set out in the Commission's Directive on GCP (see note in Section 2) and the conditions and principles for the protection of clinical trial subjects, which are proposed in Schedule 1 to the draft Regulations. Schedule 1 would be based on Articles 3 to 5 of the Directive. These principles and conditions reflect the current guidance on Good Clinical Practice that has been the accepted standard for clinical trial conduct in the EU since 1997². These standards currently provide the basis for voluntary GCP inspections and would be the basis for GCP inspections under the new Regulations for all clinical trials. Thus the new Regulations would not introduce major changes to the conduct of commercial clinical trials. Although the new Regulations do not introduce significant changes to the principles of GCP governing the conduct of clinical trials, they would make compliance with the principles of GCP a legal obligation and provide for compulsory GCP inspections.

² Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)

3.1.5 Inclusion of subjects unable to give informed consent

The Regulations would set out specific criteria that must be met before subjects are entered into a clinical trial and more stringent criteria that would apply in the case of adults incapable of giving informed consent and minors. These groups would be allowed to be included in clinical trials in the UK if they meet the specific criteria proposed in Schedule 1.

3.1.6 Change to application for ethics committee opinion

Currently, anyone wishing to conduct a clinical trial on a medicine for human use involving NHS patients or facilities must obtain a favourable opinion from an ethics committee. In addition, it is good practice to obtain an opinion in relation to private trials not involving NHS patients or facilities. Where the trial is to be conducted in five or more centres they must obtain the favourable opinion of a Multicentre Research Ethics Committee (MREC), which may take advice from a Local Research Ethics Committee (LREC) on the suitability of the investigator and facilities.

The new legislation would introduce a new system of establishing or recognising ethics committees under a UK Ethics Committee Authority. The Regulations would also set out the duties of an ethics committee in reaching its opinion. For trials conducted at more than one site it would require a single ethics committee opinion and for trials conducted in more than one European member state, a single opinion for the UK. The new legislation would set out the procedure for an investigator to apply for an ethics committee opinion and to apply to amend the conditions of the trial and would set statutory time limits for the ethics committee to respond to a request for an opinion. A single individual would therefore be responsible for obtaining an ethics committee opinion in relation to a multi-centre trial.

3.1.7 Change to application for authorisation

Under the current CTX system applicants must provide the MCA with summaries of information on manufacture and its control as well as data to support the product's specification. In addition they must provide summary data from the pre-clinical tests performed and from any clinical trials already conducted. The proposed Regulations and the guidelines from the Commission would require similar amounts and levels of information to those currently required to support an initial application for authorisation for a new Investigational Medicinal Products (IMP). Once the product is authorised for use in one trial a simplified application could be submitted for all further trials with the same products. Similarly, applications in respect of existing licensed products would require a simplified level of information where the product is to be used in a trial in accordance with the marketing authorisation.

3.1.8 Change to studies in healthy volunteers

Studies on healthy volunteers are exempt from the provisions of the Medicines Act because the definition of a clinical trial does not include studies on subjects where there is no evidence that the medicinal product will have effects which may be beneficial to the subject. Under the new legislation these studies would be considered to be clinical trials and would require an authorisation.

3.1.9 Change to amendments procedure

After commencement of a trial, under the current system the certificate or exemption holder can vary the conditions of the trial by notifying the MCA and receiving an authorisation. The new Regulations would provide for a similar system but would also place a statutory limit on the time for the MCA to respond. The new Regulations would also allow a sponsor to take urgent safety measures to protect subjects against any immediate hazard prior to informing the LA but require them forthwith to inform the LA of the details of the hazard and the measures taken. It would also allow the MCA to make a compulsory change to the conditions of the authorisation but provide the applicant with an opportunity to respond to the request for change. Finally, the new legislation provides for suspension or termination on grounds that MCA has information raising doubts about the safety or scientific validity of the trial, or that the conditions of the authorisation are not being met, which are broadly similar to those under the existing legislation. However, under the new legislation the Licensing Authority would have to inform the sponsor of its intention to suspend or terminate the trial and give them an opportunity to respond. The new legislation also would include an appeal procedure against a decision to suspend or terminate a trial and for compulsory amendments (see Section 5.4 for details).

3.1.10 Change to manufacturing and import requirements

The current system allows the supply of an IMP for a clinical trial where it is manufactured or imported in accordance with the specification submitted to the MCA as part of an application for a CTC or exemption. Under the new legislation the manufacturer would also have to obtain a manufacturing authorisation to produce IMPs and would have to have a qualified person (QP) certify that they were manufactured to Good Manufacturing Practice (GMP) standards before releasing them. The new legislation therefore would introduce the requirement that manufacturers produce IMPs to GMP standards. It also would ensure that these standards are met by providing for GMP inspection. Similarly, importers would require a authorisation and would have to be able to provide assurance that the products were manufactured to GMP standards set out in the Directive and its detailed guidelines. Manufacturers would be barred from supplying IMPs to the investigator or his team, or any trial subjects, before the trial has received authorisation. However, there are exemptions in certain hospital and health centre trials and also for reconstitution prior to administration (see 5.8.3 below).

3.1.11 Change to pharmacovigilance

To protect subjects in clinical trials, the current legislation requires that holders of a CTC or an exemption must report all suspected unexpected serious adverse reactions (SUSARs) to the MCA. Under the new legislation the reporting requirements would be similar except that it also would require a sponsor to provide a safety update once a year, which includes all suspected serious adverse reactions. It also would require investigators to report all adverse events to the sponsor. Furthermore, the new legislation would require the UK to exchange information about safety by ensuring

that all SUSARs brought to its attention are entered into a pharmacovigilance database at the European Medicines Evaluations Agency (EMEA). This database would be accessible only to the Member States, the Commission and the EMEA. The new Regulations would require sponsors to report SUSARs to the Licensing Authority. However, this may be achieved by submitting the reports electronically to the EMEA database gateway from where they would be sent to the MCA. This proposed procedure would avoid duplicate reporting both to the Member States and to the EMEA database while ensuring that all the safety information is available. The design of the EMEA database would allow sponsors to report SUSARs via a website link and companies to report directly by transfer from their own database. This proposal would reduce any unnecessary duplicate reporting and would facilitate the monitoring of safety in clinical trials.

4. Scope of the Regulations and Definitions

4.1.1 Scope

The scope of the Directive is wide and therefore the scope of the Regulations would be wide, covering the conduct of clinical trials on human subjects involving medicinal products (as defined in Directive 2001/83/EC) including trials involving healthy volunteers. In effect, every clinical trial concerned with ascertaining the safety or efficacy of a medicinal product would be covered including comparisons of efficacy between existing products. This would include both commercial and non-commercial research, and whether it takes place within or outside the NHS.

4.1.2 Non commercial clinical trials of medicines

The Directive does not distinguish between trials for commercial purposes (such as licensing) and those funded from non-commercial sources for public benefit (such as comparative trials of products that have a marketing authorisation). In either case, the Regulations would require the sponsor to comply with good clinical practice and to put and keep in place arrangements to ensure that good clinical practice is adhered to; and to undertake tasks such as applying to the licensing authority for authorisation for a trial. As now, a sponsor may engage other individuals or organisations to carry out, on behalf of the sponsor, various activities in relation to a trial; for example, a contract research organisation. This could include developing and operating the arrangements to ensure GCP compliance required by the Regulations. The relevant individual or organisation would themselves have a responsibility for complying with GCP; and the sponsor would remain responsible for ensuring that the arrangements with that other individual or body were working effectively.

4.1.3 Definitions

The proposed definitions in Regulation 2 are concerned with the interpretation of the draft Regulations and would include a list of definitions of the words or terms used in the draft legislation. Many of these are drawn from the Directive, while other terms have the same meaning as they have in the existing legislation (the Medicines Act 1968). A number of terms are important to understanding the scope and application of the Regulations and are explained below.

4.1.4 Clinical trial

A clinical trial is defined in the Directive and in Regulation 2. The proposed definition makes it clear that it is an investigation to ascertain the efficacy or safety of a medicine in human subjects: safety and efficacy of medicinal products being the concern of Directive 2001/83/EC which regulates the marketing of medicines in Europe. A clinical trial authorisation would be required for such activity. The medicine to be tested is an investigational medicinal product (IMP) and may be any product which is to be used in such a trial, either as a test product or a reference product, and a manufacturing authorisation would be required for such a product.

If healthy volunteers are administered an IMP as part of an investigation to see the effects of the drug (e.g. absorption, distribution, metabolism, excretion, etc.) or to observe any adverse reactions with the aim of determining its safety or efficacy, a clinical trial authorisation would be required for such activity.

4.1.5 Non-interventional trial

The Directive and proposed Regulations specifically exclude anything that is a 'non-interventional trial' from the definition of a clinical trial. That is a study that involves products with a marketing authorisation that are prescribed in the usual manner and used in accordance with the authorisation. Also the assignment of a patient to a therapeutic strategy must fall within current practice and must be separated from the decision to enter the patient into the study. In addition diagnostic or monitoring procedures may not be applied to the patient other than those ordinarily applied in the course of the particular therapeutic strategy. Furthermore, epidemiological methods are to be used for the analysis of the data. For example a cohort study to look for a difference between a group of patients who have been prescribed a particular medicine in the normal course of their treatment and a control group that have not; this would be a prospective non-interventional study. However, there could be no additional intervention over and above the clinical care that the patient would receive under normal circumstances for the study to remain non-interventional.

4.1.6 Role of the sponsor

In this country, there has been a tradition of collaboration between universities, NHS hosts and non-commercial funders (such as research councils and charities) in carrying out trials for public benefit. The draft Regulations would define the term "sponsor" in accordance with the Directive (see Regulation 2). The sponsor would be the individual or body who takes on ultimate responsibility for the initiation and management (or arranging the initiation and management) of, and the financing (or arranging the financing) for, that trial. A sponsor may make arrangements with other individuals or organisations to carry out, on behalf of the sponsor, various activities in relation to a trial. For example, an industry sponsor may engage a contract research organisation. The proposed definition makes clear that a body funding a non-commercial trial would not necessarily be the sponsor. It would be for those involved in the trial to establish who is to take on the role and apply to the competent authority for authorisation.

Whilst the sponsor would be allowed to arrange for the investigator or others to undertake tasks specified in the regulation, they would remain responsible for the performance of the specific obligations imposed on them by the regulations. In some cases, breach of those obligations may constitute a criminal offence, although if the breach is the fault of another person, the sponsor may be able to rely on the 'due diligence' defence in regulation 50.

There would have to be a sponsor in order to make the application to the licensing authority as required under Regulation 16. This would not prevent preparations for a trial leading up to the application, such as drafting the protocol and peer review. When taking on the responsibility, the sponsor would have to be satisfied that these preparations enable the trial to be initiated and managed in accordance with the conditions and principles of good clinical practice as set out in Part 4 of the Regulations.

The definition and role of the sponsor in the Regulations would have consequences for the Research Governance Framework for Health and Social Care published by the Department of Heath in 2001. A second edition of the Framework will be prepared in tandem with this consultation. Subject to Ministers' agreement, it is intended to finalise the second edition of the Framework when the Regulations come into force.

5 Detailed Description of the Regulations

5.1 Good Clinical Practice (GCP)

5.1.1 Standards of GCP

Good clinical practice (GCP) is a set of internationally recognised ethical and scientific quality requirements that must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects. Compliance with GCP provides assurance that the rights, safety and well being of trial subjects are protected, and that the results of the clinical trials are accurate and credible. Article 1(4) of the Directive provides that all clinical trials covered by the provisions of the Directive, including bioavailability and bioequivalence studies, shall be designed, conducted and reported in accordance with the principles of GCP. The draft UK Regulations provide for the implementation of Articles 1(4) and 3 to 5 of the Directive by requiring that the conditions and principles of GCP must be complied with (Regulation 26 and Schedule 1).

Regulation 26 requires that no person shall conduct a trial or carry out the functions of the sponsor of a trial (whether they are actually the sponsor or acting under arrangements made with the sponsor e.g. a contract research organisation), other than in accordance with the conditions and principles of GCP. In addition, the sponsor would have a duty to put and keep in place arrangements to ensure that GCP is being complied with. The term "conditions and principles of good clinical practice" is defined in Regulation 2(1), so as to include both those conditions and principles listed in Schedule 1 and the principles listed in the draft Commission Directive on GCP ENTR 6416, the latest version of which is available on the EU Commission website "www.pharmacos/eudra.org".

The legally enforceable principles of GCP which apply to clinical trials covered by the provisions of the Directive, are contained in the draft Commission Directive on GCP and in Schedule 1 of the draft UK Regulations.

Trials sponsors should be aware that if data from a clinical trial conducted outside the EU is to be relied on for the purpose of an application for a UK marketing authorisation, the trial must have been conducted in accordance with the principles of GCP. This is required by the relevant European Community and UK legislation (see Annex 1 to Directive 2001/83/EC and regulation 4 of the Medicines for Human Use (Marketing Authorisations Etc) Regulations 1994). Regulation 20 would support this by making it a requirement that if a sponsor applies in the UK for authorisation to conduct a clinical trial which is to be conducted also at trial sites in a third country (i.e. outside the European Economic Area), the licensing authority may require the sponsor to provide an undertaking that their premises, or any other premises at which the clinical trial is to be conducted in that third country, may be inspected by the authority for the purpose of establishing whether or not GCP is complied with at those sites.

In addition to the principles of GCP, clinical trial sponsors should take into account other applicable Community guidelines relating to the quality, safety and efficacy of medicinal products for human use and updates as adopted by the CPMP, as for example, the Note for Guidance on Good Clinical Practice (CPMP/ICH/139/95).

5.1.2 GCP inspection programme

The draft Regulations would introduce statutory powers in relation to clinical trial inspections, including GCP and Good Manufacturing Practice (GMP) inspections. The provisions of the Medicines Act relating to enforcement are extended by Regulation 46 to the provisions of the draft UK Regulations. The provisions of the Medicines Act include powers to enter, inspect and to take copies of documents and samples. The MCA plans to introduce a new programme of GCP inspections to replace the voluntary programme that has been in operation since 1997. The new programme of GCP inspections would commence when the provisions of the draft Regulations are brought fully into force (i.e. on 1 May 2004). A regular programme of GCP inspections (systems and trial-specific) would be established from clinical trial applications made to the MCA. Any specific concerns and issues raised outside the programme would trigger non-routine inspections. Inspections of commercial and non-commercial clinical research would take place and may be announced or unannounced.

In accordance with Article 15(1), any site involved in a clinical trial, particularly the investigator sites, the manufacturing sites of the investigational medicinal product, any laboratory used for clinical trial analyses and the sponsor's premises, may be subject to inspection. Contract research organisations/contractors acting under arrangements with a sponsor to perform some or all of the functions of the sponsor of a clinical trial (as referred to in Regulation 26(1)(b)), would also be subject to GCP inspection. There are no plans for the MCA to introduce an inspection programme for Ethics Committees in the UK.

Subject to any arrangements that may have been concluded between the Community and third countries, the Commission or a Member State may propose that trial site and/or sponsor's premises and/or a manufacturer established in a third country undergo an inspection (Article 15(4) and Regulation 20).

5.1.3 Enforcement of GCP

Part 8 and Schedule 7 of the draft Regulations contain details relating to the powers of inspectors, confidentiality and the penalties for non-compliance with the Regulations. Regulation 47 details the infringement notice procedure for non-compliance with specific Regulations.

The devolved administrations in the UK would have formal responsibility for enforcement in the areas covered by the administrations, but it is proposed that the MCA would enforce the new Regulations on behalf of the devolved administrations under the current arrangements for medicines control enforcement in the UK.

5.2 Consent by a legal representative on behalf of a person not able to consent

5.2.1 Persons not able to consent

Article 4 of the Directive provides that a clinical trial on minors may be undertaken only if the informed consent of the parents or legal representative has been obtained; and Article 5 of the Directive provides that a clinical trial on adults incapable of giving informed consent may only be undertaken if the informed consent of a legal representative has been obtained. Regulation 26 and Schedule 1 to the Regulations would implement these obligations. Under Regulation 26, a trial must be conducted in accordance with the "conditions and principles of good clinical practice". By virtue of the definition of "conditions and principles of good clinical practice" in regulation 2(1), these include the conditions and principles for the protection of clinical trial subjects listed in Schedule 1.

The basis for the Directive' provisions are that persons who are incapable of giving legal consent to clinical trials should be given special protection; in particular that there should be some form of independent representation of the individual's interests.

In the case of minors (i.e. persons under the age of 16), at present inclusion of the minor in a clinical trial would be subject to consent of the parent or other person with parental responsibility; and the draft Regulations do not aim to change this position. Under the draft, one of the conditions for the protection of clinical trial subjects which must be complied with by a clinical trial is that in the case of a minor, the consent of a person with parental responsibility must generally be obtained.

In respect of incapable adults, the present position in England, Wales and Northern Ireland is that medicinal interventions on a person not able to consent are lawful if the treatment is in the person's best interests; generally speaking this would be for the clinician responsible for that person's care to determine. This is, however, subject to any advance refusals of treatment made by the person before the onset of incapacity.

In accordance with the Directive provisions, the draft Regulations would introduce a new requirement that, subject to any consent to or refusal of treatment prior to the onset of incapacity, an incapable adult may only participate in a trial if their "legal representative" has given his informed consent to the subject taking part in the trial (see paragraph 4 of Part 5 of Schedule 1).

5.2.2 Legal representative

In order to comply with the Directive's provisions, paragraph 2 of Part 1 of Schedule 1 sets out who may be a "legal representative" for the purposes of the Regulations. Two types of legal representative are envisaged. The first type, who might be known as a "personal legal representative", are selected by virtue of their relationship with the person concerned, and their availability and willingness to act as the legal representative for that person (see paragraph 2(a)(i)). The second type, who might be known as a "professional legal representative", would act if no one is able to act as a personal legal representative (see paragraph 2(a)(ii)).

5.2.3 Emergency research

Most clinical trials are carried out in circumstances in which there would be time to locate a person with an appropriate personal relationship. However, research is also sometimes necessary in emergency situations – for example in cardiac arrest or the treatment of severe head injury after an accident. There is no intention in the Directive, or the implementing Regulations, to prevent such emergency research being carried out. In such circumstances, there may be little or no time to locate a personal legal representative before the intervention needs to be given.

In reaching a decision on the ethical acceptability of the trial, an ethics committee would consider the proposed arrangements for the use of legal representatives when persons not able to consent may participate in a clinical trial. It is envisaged that practical aspects of the operation of the legal representative scheme would be set out in guidance. Views are welcome on the scheme proposed for obtaining consent from a legal representative and in particular on its application in the emergency situation.

5.2.4 Scottish legislation

In Scotland, the Adults with Incapacity (Scotland) Act 2000 provides a framework within which research can involve adults not able to consent providing consent from a proxy is obtained (a guardian, welfare attorney or a nearest relative). Schedule 1, Part 1, paragraph 2(b) establishes that such persons would be the 'legal representative' for the purpose of the Regulations. However, if it is not reasonably practicable to contact a guardian, welfare attorney, or the adult's nearest relative before the decision to enter the adult in a clinical trial is made – for example in the context of emergency research – then, as in the other legal jurisdictions of the United Kingdom – it would be possible for a "professional" legal representative to give consent on behalf of that adult as described in paragraph 5.2.2. Further to 5.2.3 above, comments are welcome on this proposal and on the best approach to be taken to obtaining consent in the emergency situation in Scotland.

5.3 Applications to Ethics Committees

5.3.1 Establishment, recognition and constitution of ethics committees

Article 6 of the Directive requires that Member States take the measures necessary for establishment and operation of Ethics Committees. The Regulations (Part 2, Regulations 4 to 9 of the draft) would introduce a new statutory system for establishing and recognising ethics committees in the UK. Schedule 2 proposes additional provisions relating to the membership, meetings and proceedings, funding and staff, premises etc. of ethics committees.

5.3.2 New UK Ethics Committee Authority (UKECA)

It is proposed that under Regulation 4 a new UK Ethics Committee Authority (the 'Authority') would be responsible in the UK for establishing, recognising and monitoring ethics committees.

The Authority would not be a non-departmental public body separate from government; instead it would be a body consisting of the Secretary of State for Health, Scottish Ministers, the National Assembly for Wales and the Department for Health, Social Services and Public Safety for Northern Ireland. The Authority would act through departmental officials. The Regulations apply to ethical review of 'clinical trials' (as defined in Regulation 2), a function which forms only part of the work of existing Ethics Committees. It is proposed that those Committees, which would be recognised for the purpose of ethical review of 'clinical trials', should continue to be able, where appropriate, to accept and review proposals concerning other sorts of research, as at present.

The constitution of the Authority would be similar to other existing arrangements for other authorities such as the licensing authority under the Medicines Act 1968, the National Radiological Protection Board established by section 1 of the Radiological Protection Act 1970 and the Good Laboratory Practice Monitoring Authority (see S.I. 1999/3106). In addition to the Authority itself, it is envisaged that the Authority would make arrangements with other public bodies to carry out its functions in relation to establishing and recognising ethics committees; for example, these bodies could include NHS bodies, such as the Strategic Health Authorities which currently establish, recognise and support local research ethics committees in England (see Regulation 4(5) to (7) of the draft).

The Authority itself would have the powers to establish an ethics committee and determine the area where it operates and the kind of clinical trials it can give an opinion on. In certain circumstances it would be allowed to abolish an ethics committee or vary operating conditions.

The Authority would also have the powers to recognise an ethics committee established by another relevant authority as long as it meets the UKECA requirements for the constitution and operation of an ethics committee. The Authority could monitor ethics committees and could provide advice and assistance.

5.3.3 Ethics Committee opinions on clinical trials

Article 6 of the Directive requires an ethics committee to give an opinion before a clinical trial commences and sets out certain documents and particulars that it must consider in reaching that opinion (see paragraphs (2) and (3)). Under Regulation 14, an ethics committee which has been established or recognised under the Regulations and which receives a valid application for an ethics committee opinion from the chief investigator or the principal investigator in the case of a single site, would then give an opinion on the trial. Only if its opinion is favourable could the trial commence. In reaching its opinion, an ethics committee would be required to take into account various matters; in particular it would be required to consider the matters listed in Regulation 14(6), which is based on the list of matters to be considered by ethics committees contained in Article 6 of the Directive. The matters which the committee must consider include, but are not limited to:

- relevance and design of the trial, and anticipated risks and benefits
- investigator's brochure and trial protocol
- suitability of the investigator(s), of supporting staff and of the quality of the facilities
- arrangements for recruitment of trial subjects, and written or other information to be given to the participant
- procedure for obtaining informed consent
- justification of the research on persons incapable of giving informed consent
- provision of indemnity or compensation in the event of injury or death attributable to a clinical trial such as the system of financial liability for clinical negligence known as NHS indemnity_
- any insurance or indemnity to cover liability of investigator and sponsor
- amounts and arrangements for rewarding or compensating investigators and trial subjects
- certain aspects of the agreements between the sponsor and the trial site.

As now, an ethics committee would have to consider any other matter which is relevant to the ethical approval of the trial in question. Furthermore, in accordance with Regulation 14(9) of the draft, an ethics committee would be obliged to consider and give an opinion on any other issue relating to the clinical trial if raised by the applicant and it appears to the committee to be relevant to the ethical consideration of that trial.

Regulation 15 would provide a mechanism whereby a chief investigator who is dissatisfied with an unfavourable ethics committee opinion may request that the Authority direct another ethics committee to consider his application

5.3.4 Statutory time periods

Under the draft Regulations, an ethics committee would have to give an opinion within 60 days of receipt of a valid application, unless a longer period is allowed for under Regulation 14 (see the definition of "specified period" in Regulation 14(10)). In the case of clinical trials involving medicinal products for gene therapy and

somatic cell therapy, or a medicinal product containing a genetically modified organism, an extension of 30 days would be allowed and the ethics committee would have a total of 90 days to consider the case. A further extension of 90 days, giving a total of 180 days, would be allowed for these trials where, in accordance with Regulation 14(4), the ethics committee consults a group or committee in order to consider such trials. In giving its opinion an ethics committee would be allowed to ask applicants once for supplementary information. During the period from when the ethics committee makes the request to when it receives the information the 60/90/180-day period would be suspended.

5.3.5 Opinions for multi-centre trials

Article 7 of the Directive requires that Member States establish a procedure to obtain a single opinion for multi-centre trials. For multi-centre trials conducted inside the UK (irrespective of whether they are also being conducted in other countries), Regulation 13 would set out the ethics committee to which an application must be made in the case of a multi-centre trial – i.e. to an ethics committee established or recognised for an area in which the chief investigator is "professionally based", or for the entire UK, and which is responsible for considering the type of clinical trial in question.

5.3.6 Amendments

Article 10(a) of the Directive sets out a procedure for amending the protocol of a clinical trial. In relation to amendments, the ethics committee would have to give an opinion on any amendment which involves changes to the clinical trial protocol or any other particulars or documents which accompanied an application for an ethics committee opinion (see Regulations 10, 22 and 23).

5.3.7 Adverse events

In relation to adverse events etc. an ethics committee would have to receive reports of suspected unexpected serious adverse reactions and an annual report of serious adverse events with a report on the subjects' safety (see Regulations 31 to 34).

5.3.8 Guidance on applications to ethics committees

Under Regulation 13(5), applications to an ethics committee for an opinion would have to be made in writing and accompanied by the particulars and documents which are to be listed in the Commission guidelines referred to the consultation document. A draft guidance note, which indicates the general format and content of an application for an ethics committee opinion, is available on the EU Commission website "www.pharmacos/eudra.org".

5.4 Applications to the Competent Authority

5.4.1 Requirements to commence a clinical trial

Under the new legislation, the LA, as defined in regulation 2(1), is the licensing authority established under section 6 of the Medicines Act, which acts by the MCA,

and is responsible for medicines licensing and the existing clinical trials regime, would be the Competent Authority for the UK and would therefore be responsible for considering requests for authorisation to conduct clinical trials. Before commencing a clinical trial a sponsor would have to receive authorisation from the LA and a favourable opinion from an ethics committee. If the LA refuse an application for authorisation, or accept it subject to conditions, there is a procedure for referral to the Committee on Safety of Medicines (the "appropriate committee") and the Medicines Commission, set out in Regulation 25 and Schedule 3 and paragraph 5.13 below.

Nobody would be allowed to start or conduct a trial until the trial had been authorised by the licensing authority (see Regulation 11) and to start or conduct a trial otherwise would amount to a criminal offence under the Regulations. In addition, Regulation 12 would control the supply of medicinal products for use in clinical trials. In particular it would provide that products should not be sold or supplied to the investigator or other person conducting a trial, or to a trial subject, unless the sponsor has been authorised to conduct a trial with that product (unless it is sold or supplied in accordance with the terms of a marketing authorisation relating to that product) and the product has been manufactured or imported by a person holding a manufacturing authorisation in the UK or EEA. To supply a product otherwise would also amount to a criminal offence under the Regulations.

5.4.2 Request for authorisation of a clinical trial

Under Regulation 16 a request for authorisation of a clinical trial would be made to the LA by the sponsor in writing and signed by or on behalf of the applicant. In practice the sponsor would make an application in English to the Medicines Control Agency (MCA). The format and content of these applications to the UK competent authority are described in a draft Commission guideline which can be accessed at www.pharmacos/eudra.org.

5.4.3 Classes of medicinal products

The Regulations would recognise three different classes of medicinal product and would provide different rules for each; they would provide more lengthy periods of consideration for some of these. The classes are:

- a) general medicinal products (Regulation 17), (that is those that do not fall into class b) and c) that follow),
- b) medicinal products for gene therapy and somatic cell therapy, including xenogeneic cell therapy and medicinal products containing genetically modified organisms (Regulation 18), and
- c) medicinal products with special characteristics such as biological products of human or animal origin or containing components from those origins or whose manufacture requires such components (Regulation 19) and do not have a marketing authorisation within the meaning of Directive 2001/83/EC.

5.4.4 Authorisation procedure for clinical trials with general medicinal products

Regulation 17 would establish a procedure for authorisation of clinical trials with general medicinal products including time limits for the sponsor and the licensing authority. There are three parts to the procedure following receipt of an application.

- Firstly the LA, within the period of 30 days, may write to the sponsor giving notice of grounds for not accepting the request. If no such notice was given within that period the clinical trial would be treated as authorised. Alternatively the LA may notify the sponsor that it accepts the request subject to the condition in the notice (see Regulations 17 (2) to (4)).
- Secondly, the sponsor may within the period of 14 days (or an extended period allowed by the LA) from the date of receipt of the notice of grounds for not accepting the request send an amended request to the LA for further consideration. If no such amended request is submitted the request would be considered rejected and the LA would not consider any further amendments to the request (see Regulation 17 (5)).
- Thirdly, when the LA receives an amended request, they would have to give written notice to the sponsor within the period of 60 days from the date on which the original request was received that there are grounds for not accepting the request. The request would be treated as rejected and the LA would not consider any further amendments. If the LA does not send such a notice the clinical trial would be treated as authorised (see Regulations 17 (6) to (8)).

5.4.5 Authorisation procedure for clinical trials involving products for gene therapy and somatic cell therapy, including xenogeneic cell therapy and medicinal products containing genetically modified organisms.

The proposed authorisation procedure for medicinal products for gene therapy and somatic cell therapy including xenogeneic cell therapy, and medicinal products containing genetically modified organisms is contained in Regulation 18. The procedure has the same three parts as for general medicinal products above except the time periods would be lengthened. The LA would have to issue a written authorisation and could not authorise the clinical trial by allowing the LA's time period for response to run out (see Regulation 18(2)(a) & 18(7)(a)). In the case of xenogeneic cell therapy products the LA could issue a written authorisation of grounds for not accepting the request at any time after the receipt of a request (see Regulation 18(9)). There would also be a provision to refer the request to a relevant committee (see Regulation 18(4)(5)&(7)). In practice that could be the Committee on Safety of Medicines or a committee that has specialist knowledge of the class of the relevant products or their use in therapeutic strategies.

- For the first part of the procedure the LA would have to respond to the request within the period of 30 days (see Regulation 18(2)). However when it refers the request to a relevant committee the LA would have to respond to the request within the period of 120 days (see Regulation 18(5)).
- For the second part of the procedure the sponsor could submit an amended request within a period of 30 days from receipt of a notice of grounds for not

- accepting the request or such extended period that the LA could allow (see Regulation 18(6)).
- For the third part of the procedure the LA would have to give written notice of grounds for not accepting the request within a period of 90 days from the original receipt of the application or where it has referred the request to a relevant committee within a period of 180 days from the original receipt of the request (see_Regulation 18(7)). Alternatively, they could issue a written authorisation to the sponsor subject to the conditions in the notice (see Regulation (7)(a) & (8)).

5.4.6 Authorisation procedure for clinical trials involving products with special characteristics other than 5.2.5

The proposed procedure is set out in Regulation 19. It has the same three parts as for general medicinal products as described above except that the LA would have to issue a written authorisation and could not authorise the clinical trial by allowing the LA's time period for response to run out (see Regulation 19(2)(a) & (4)(a)). The products with special characteristics would include those which do not have a marketing authorisation and are referred to in Part A of the Annex to Regulation (EEC) No. 2309/93 that is medicinal products developed by means of one of the following biotechnological processes:

- recombinant DNA technology,
- controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells,
- hybridoma and monoclonal antibody methods, and

have an active ingredient that:

- is a biological product of human or animal origin, or
- contains biological components of human or animal origin, or
- requires such components in its manufacture.

In addition the LA could notify the sponsor of its need to issue a written authorisation for a clinical trial within a period of 7 days of receipt of a request for authorisation of a clinical trial involving a product with special characteristics other than those described above (see Regulation 19(1)(b)).

5.5 Amendments to clinical trials authorisation

5.5.1 Notification of amendments

Regulation 21 proposes two procedures to amend the conditions of a clinical trial authorisation: a) by the licensing authority, b) by the sponsor after the LA has written to them to accept the amendment.

5.5.2 Amendments by the licensing authority

Regulation 22 proposes that the licensing authority may compulsorily amend the conditions of a clinical trial authorisation. However, before doing so it would have to notify the sponsor at least 14 days before the date on which it is proposed the

amendment should take effect. The sponsor could then respond in writing before the proposed amendment is to take effect and the LA would take those responses into account before deciding to make the amendment.

5.5.3 Amendments to take urgent safety measures

Regulation 28 proposes that the sponsor and investigator may take appropriate urgent safety measures in order to protect subjects in a trial against immediate hazard to their health and safety from new events related to the conduct of the trial. As proposed, the sponsor would have to immediately and no later than 3 days after the measures are taken inform the LA in writing of those events and the measures taken and inform the ethics committee which gave the original opinion for the trial. Failure to do so would be a criminal offence.

5.5.4 Amendments by the sponsor

Regulation 23 proposes that a sponsor can make amendments to the clinical trial authorisation. However if they wish to make a substantial amendment to the protocol and/or to the information in documents that accompanied the request for authorisation would have to send a notice of amendment to the LA and in the case of amendments to the protocol, to the ethics committee which gave the original opinion for the trial.

5.5.5 Definition and examples of substantial amendments

Regulation 10 proposes a definition of a substantial amendment to a clinical trial authorisation as one that is likely to affect to a significant degree:

- The safety and personal integrity of the subjects of the trial,
- The scientific value of the trial,
- The conduct and management of the trial
- The quality or safety of an IMP used in the trial.

Amendment to the conduct and management of the trial: A substantial amendment to the conduct of the trial could be a change to: the measures of efficacy, the inclusion or exclusion criteria, the number of participants, the age range of participants, duration of exposure to the product, safety monitoring procedures which would be part of the protocol. In addition, a substantial amendment to the management of the trial could be a change to: the facilities for the trial, the chief investigator, the financial agreements related to the trial or the indemnity or insurance arrangements for the sponsor, investigators or trial subjects.

Amendment to the quality or safety of an IMP used in the trial: A substantial amendment to the quality of the IMP could for instance be a change to: the manufacturing process for the active substance, specification of the active substance or the medicinal product, test procedures for the active substance or medicinal product, of the immediate packaging material or of the shelf life that was provided in the IMP dossier. In addition_a substantial amendment to the safety of an IMP used in the trial could be results or new interpretation of toxicity tests or pharmacology tests, or results of new interaction studies. Alternatively it could be the results of new clinical trials or new pharmacology tests, new interpretation of existing clinical trial data, or safety related to a clinical trial with the product.

Further examples of what might be considered a substantial amendment are listed in the draft Commission guideline ENTR 6418 which is available on the EU Commission website "www.pharmacos/eudra.org".

5.5.6 Procedure for modifying or adapting rejected proposals for amendment

Regulation 24 proposes a procedure whereby the sponsor should be able to modify or adapt a notice of amendment that has been rejected by the LA or not given a favourable opinion by the relevant ethics committee to take account of their concerns and resubmit it. The sponsor would have to give a notice in writing to the LA and/or the relevant ethics committee at least 14 days before they intend to make the amendment (see Regulation 24 (2)). The LA would be allowed within the period of 14 days from the date of receipt of the notice to give written notice to the sponsor of any further grounds for not accepting the modified or adapted amendment. Similarly, the relevant ethics committee would be allowed within 14 days from the date of receipt of a modified or adapted notice of amendment to give a written notice to the sponsor stating that its opinion of the adapted amendment is unfavourable. If the sponsor does not receive such a noticetheymay make the modified or adapted amendment.

If the LA refuse an application for an amendment, or accept it subject to conditions, there is a procedure for referral to the Committee on Safety of Medicines (the "appropriate committee") and the Medicines Commission, set out in Regulation 25 and Schedule 3 and paragraph 5.13 below.

5.5.7 Conclusion of a clinical trial

The sponsor should specify when they expect the trial to end in the protocol submitted for trial authorisation. Regulation 30 would require the sponsor to notify the LA in writing and the ethics committee that gave the original favourable opinion that the trial has ended. The notification would have to be within a 90-day period from the conclusion of the trial. However, if the sponsor concluded the trial before the date or event when the protocol indicated the trial would end, the notification would have to be within a period of 15 days and include an explanation of the reasons for terminating the trial early. Anyone contravening this Regulation would be guilty of a criminal offence.

5.5.8 Infringement notices relating to clinical trials

Article 12(2) of the Directive provides that where a competent authority has objective grounds for considering the sponsor or the investigator or any other person involved in the conduct of a trial no longer meets the obligations laid down, it shall inform them, indicating the course of action which they must take to remedy this state of affairs. In such a case, the competent authority must inform the relevant ethics committee, the Competent Authorities in all other Member States and the Commission of the required course of action. This Directive provision would be implemented by regulation 47 of the draft Regulations, which would confer on the licensing authority a power to issue an infringement notice, informing a person of the measures which they must take in order to ensure that a breach of the Regulations

does not continue or does not recur, and requiring him to take such measures within a specified period of time.

5.6 Suspension or termination of a clinical trial

5.6.1 Procedure for suspension or termination of a clinical trial

In accordance with the provisions of Article 12(1) of the Directive, the Regulations propose to give power to the LA to suspend or prohibit a clinical trial either generally or at a particular trial site where it has grounds for considering that the conditions of the request for authorisation are no longer met, or has information raising doubts about the safety or scientific validity of the trials or the conduct of the trial at a particular site (see Regulation 29). When the LA intends to issue such a notice it would have to notify the sponsor or investigator in writing within one week of the date of the intended notice that they were minded to issue such a notice and the reasons why except where there is an imminent risk to the health or safety of any of the subjects of the clinical trial (see Regulations 29(5) & (6)). They would also have to advise the sponsor that they may within one week of the notice furnish the authority with written representations of whether the trial or the conduct of the trial at a particular site should be suspended or terminated.

If the LA issued a notice to suspend or prohibit a clinical trial they would be required to notify the sponsor or the investigator at each trial site that they should suspend or terminate the trial or its conduct at that particular site. It is proposed that the notice would specify whether the notice applies generally or to one or more sites and whether it requires suspension or termination. If the notice requires suspension it would specify whether the suspension is to take effect immediately or on a date specified in the notice and whether it applies until further notice from the LA or for a period specified in the notice. It would also specify any conditions which are to be satisfied before the trial may be recommenced. If the LA issued such a notice it would have to immediately inform the competent authorities of each EEA State, the relevant ethics committee that gave the original favourable opinion, the EMEA and the European Commission. The appeal procedure relating to suspension or termination of a clinical trial is described below at Section 5.13 and in Schedule 3 of the Regulations. However where the notice of suspension or termination is referred to an appropriate committee or the Medicines Commission it would remain in force unless revoked in accordance with Schedule 3.

5.7 Exchange of information

Article 11(1) of the Directive requires the EEA States to enter into a European Database, extracts from the request for authorisation, any amendments to the request, amendments to the protocol, the favourable opinion of the ethics committee, the declaration of the end of the clinical trial and a reference to inspections on conforming with good clinical practice. Also, Article 11(2) requires the LA to supply all information further to that in the European Database to any EEA State, the Agency or the Commission when they make a substantiated request for it. The proposed operation of the European clinical trials database that would allow this is described in the draft Commission guideline ENTR-6421 which is available on the EU Commission website www.pharmacos/eudra.org.

5.8 Manufacture and importation of investigational medicinal products (IMPs)

5.8.1 IMP manufacturing authorisations

In accordance with the provisions of Article 13 of the Directive, all persons intending to manufacture, assemble and/or import IMPs would be required to hold a manufacturing authorisation in accordance with Regulation 35 (1) and it would be an offence to carry out these activities without a manufacturing authorisation after 1 May 2004 (Regulation 48 (h)).

The MCA proposes to issue one manufacturing authorisation called an "IMP Manufacturer's Licence", that covers the manufacture, assembly and/or importation of an IMP. Each particular authorisation would only cover the manufacturing, assembly or importation activity as specified by the applicant in his application. IMP manufacturer's licences, as with existing manufacturer's licences, would contain standard provisions imposing various detailed obligations on the holder. The proposed draft standard provisions for manufacturers and importers are set out in Part 2 and Part 3, respectively, of Schedule 5 to the Regulations.

The holder of an IMP Manufacturer's Licence would be obliged to comply with the principles and guidelines of good manufacturing practice (GMP), as laid down in Commission Directive 91/356/EEC as amended and the Standard Provisions specified in the Regulations (Regulation 41 (a) & (b)).

An IMP Manufacturer's Licence, under the draft Regulations, would only cover the manufacture, assembly and/or import of products for the purpose of clinical trials. Following the completion of a clinical trial the manufacture, assembly and/or importation of medicinal products to meet compassionate need, supplied in accordance with Schedule 1 to the Marketing Authorisation Regulations, must be carried out by organisations holding a Manufacturer's Licence or Manufacturer's Specials Licence or, in the case of import, by a person holding either a full Wholesale Dealers Licence or a Wholesale Dealers Import Licence, in accordance with the relevant provisions (SI 1999/04).

5.8.2 Import and export of investigational products

An importer of IMPs imported from third countries would require an IMP Manufacturer's Licence. An IMP Manufacturer's Licence would also be required where IMPs manufactured in the UK are intended for export to third countries, for use in a clinical trial.

5.8.3 Exemptions from IMP Manufacturer's Licences

In certain cases exemptions from the need to hold an IMP manufacturing authorisation would apply. These would be available where repackaging or other changes to the packaging of an IMP is done in a hospital or health centre by a doctor, pharmacist or person acting under the supervision of a pharmacist and where the IMPs are for use in that hospital or health centre (Regulation 36 (1) and (2)). An

exemption may be terminated where the hospital or health centre does not have the staff, premises, equipment or facilities to carry out changes to packaging or repackaging processes properly. It can also be terminated where it is considered that the IMP can no longer be safely administered or is not of satisfactory quality as a result of the changes to packaging or repackaging processes (Regulation 36 (3) (a) and (b). In addition the reconstitution of IMPs (dissolving or dispersing the product, or diluting or mixing it with, some other substance to be used as a vehicle for the purpose of administering it) prior to administration (e.g. reconstitution within a hospital) would not constitute manufacture and would not require an authorisation (the definition of "manufacture" is that used in the Medicines Act).

5.8.4 Revocation or suspension of an IMP manufacturing authorisation

The MCA may revoke, vary or suspend an IMP manufacturing authorisation when a statutory condition of the authorisation is no longer being met (Regulation 44 (1)). The MCA would give the authorisation holder notice of its proposals and set out the reasons. In most cases the authorisation holder would be given a period of not less than 28 days to respond. The authorisation holder may give notice to the MCA of his desire to be heard by a person appointed for the purpose, or make written representations to the Licensing Authority with respect to its proposals (Schedule 6).

Where it appears to the MCA that public safety is at risk it may suspend an IMP manufacturing authorisation with immediate effect or from a specified date for such a period as the MCA may determine without prior notification to the holder (Regulation 44 (1) and paragraph 6 of Schedule 6).

5.8.5 Transitional arrangements

In order to ensure a smooth transition from the current position to one of regulation of manufacture/import, it is proposed that the final version of the Regulations would include provision so that persons may apply for the appropriate authorisation before 1 May 2004. This is in order to avoid the situation where the approval of a trial is delayed because the site of manufacture/importation has not been licensed. The proposal is that it would be possible to submit applications for an IMP manufacturing authorisation from the date the relevant provisions of the Regulations were brought into force, some time later this year. You are invited to comment on proposed arrangements. These authorisations may be granted or refused following an assessment procedure of the application, which may include an inspection (Regulations 38 and 46).

5.9 Qualified Persons

5.9.1 Certification by a Qualified Person

Article 13 (2) of Directive 2001/20/EC requires that the holder of an IMP manufacturing authorisation must appoint at least one Qualified Person (QP), to be named on an IMP manufacturing authorisation. The QP's duties are specific and are intended to ensure that every batch of an IMP has been manufactured and/or assembled and checked in accordance with the requirements of Commission

Directive 91/356/EC laying down the principles and guidelines of good manufacturing practice for medicinal products for human use as amended, the product specification file and information notified in the application for a clinical trials authorisation. The Directive's provisions relating to QPs are implemented primarily by regulation 42.

A QP has a personal responsibility for ensuring that the required tests and controls are carried out and must sign or certify, for each batch, that the appropriate tests have been carried out and that it complies with the relevant clinical trials authorisation. The QP must ensure that the register or record is regularly maintained and that entries are made as soon as practicable after each batch has been manufactured and before the batch is released for use in a clinical trial.

An IMP manufacturing authorisation application would require the naming of at least one Qualified Person (Regulation 42 (1)). As part of the assessment of the application for a authorisation the MCA would consider the suitability of the person taking into consideration their qualifications and relevant experience (see regulation 42(1) and paragraph 5 of Schedule 6).

Detailed guidance on those elements that need to be taken into account prior to the certification of a batch within the Community would be set out in Commission Directive 91/356/EEC, laying down the principles and guidelines of good manufacturing practice for medicinal products for human use, as amended and in particular Annex 13, referred to in Article 47 of Directive 2001/83/EC and Article 13 of the Clinical Trials Directive.

5.9.2 Definition of a qualified person

A QP must satisfy the requirements of Article 49 or 50 of Directive 2001/83/EC in respect of qualifications and experience. The QP must be a member of the Institute of Biology, the Royal Pharmaceutical Society of Great Britain, or the Royal Society of Chemistry, or another body considered by the LA to be appropriate for these purposes.

Where a person does not satisfy the requirements of Article 49 or 50 of Directive 2001/83/EC they may be considered to be eligible if;

- they are performing the duties of a QP in respect of investigational medicinal products for a period from 1 May 2003 to the date of the valid application for a manufacturing authorisation in respect of which the person is to act as a QP or the 30 April 2004, whichever is earlier and will have 12 months experience on or before the date of issue of the licence or
- they were engaged in such activities on the date of the application for a manufacturing authorisation or 30th April 2004, whichever is earlier, or
- has been named as a qualified person in a valid application for a manufacturing authorisation for IMPs made prior to 1st May 2006.

It is proposed that transitional arrangements would be included in the draft Regulations so as to provide that a person who carries out the testing and other activities which must be carried out by a QP under the draft Regulations, prior to the coming into force of the Regulations, would be able to act as a QP under the new provisions providing certain criteria are met. The relevant provision in the draft is paragraph (b) of the definition of "qualified person" in regulation 2 (1).

5.10 Labelling of investigational medicinal products

Details concerning the labelling of IMPs are to be found in Annex 13 of the GMP guidelines, Directive 91/356/EEC. Draft Regulation 45 provides that an IMP must be labelled in compliance with the obligations which relate to that product by virtue of Article 14 of the Directive. This would mean that the labelling of IMPs would have to comply with the guidelines on labelling adopted under Article 14, which are to appear in a revised Annex 13.

It would be a criminal offence for a sponsor to sell or supply, or procure the sale or supply, of an IMP to a trial subject or a person administering the product in the trial, if it were not properly labelled in accordance with those requirements.

Similarly, it would be a criminal offence for any other person to sell or supply such a product to a subject or a person administering the product in the trial, if they knew or had reasonable cause to believe that the labelling does not comply with these requirements.

5.11 Pharmacovigilance

5.11.1 New requirements

Sponsors are already required by secondary legislation under the Medicines Act to report serious unexpected adverse reactions that occur during a clinical trial to the licensing authority. Articles 16 and 17 of the Directive require the reporting of such reactions, but impose additional obligations. These Articles would be implemented by Regulations 31 to 34 of the draft Regulations. In particular they provide for notification of serious adverse events, as well as the reporting of suspected unexpected serious adverse reactions. The provisions would set out the new requirements as to the procedures for, and times within which, such reports must be made. In addition, they would impose a requirement on the sponsor to provide an annual list of all serious adverse events (expected and unexpected) and a report on the safety of subjects participating in the trial.

5.11.2 Required reports

Regulation 31 would require the investigator to report all serious adverse events immediately to the sponsor (unless the protocol or investigator's brochure indicates that they do not need to be reported immediately and to follow this with a detailed written report). These reports would have to use unique code numbers to identify the

subjects. Where the protocol requires certain adverse events and /or laboratory abnormalities to be reported in a specified manner or timeframe, the investigator would have to report them to the sponsor in accordance with those requirements. In the case of reports of deaths the investigator would have to provide the sponsor and ethics committee with any additional information they require. The sponsor would have to keep detailed records of all adverse events reported to him by the investigator relating to a clinical trial and the LA would be allowed to require him to send the records, or a copy of the records, to the authority by sending him a notice in writing.

5.11.3 Notification of suspected unexpected serious adverse reactions (SUSARs)

Regulation 32 would require the sponsor to record all relevant information about SUSARs and report it to the LA, to the competent authorities of any EEA State in which the trial is being conducted and the relevant ethics committee within a specified period measured from the sponsor's first knowledge of the reaction. For fatal and life threatening SUSARs the period would be 7 days for the initial report and a further 8 days for additional relevant information. For all other SUSARs the period would be 15 days. The sponsor would also have to inform each of their investigators responsible for the conduct of a trial (see Regulation 32(5)) with that IMP. Article 18 of the Directive requires the Commission to publish guidance on the collection, verification and presentation of adverse event reaction reports together with decoding procedures for SUSARs. This is available in the draft Commission guideline ENTR-6422 which is available on the EU Commission website www.pharmacos/eudra.org.

5.11.4 EU pharmacovigilance database

Article 17(3)(a) of the Directive requires each EEA State to ensure that all SUSARs brought to its attention are entered into the European database established in accordance with Article 11(1) of the Directive. Under Regulation 32(6), if a SUSAR relating to a medicinal product were brought to the attention of the LA, they would have to record it and ensure that the details are entered in the above European database either by the sponsor or by the LA. Under Regulation 32(4) the sponsor may ensure that a report or information is sent to the LA and the competent authorities of any EEA State, by entering the report or information into the above European database. Since the EEA States, including the UK, would have access to the database in accordance with Article 11(1) of the Directive and the EMEA are required to make the information notified by the sponsor available to the competent authorities of the EEA States in accordance with Article 17(3)(b) of the Directive, the procedure proposed in Regulation 32(4) would ensure that any report by a sponsor to the European database could be accessed by LA and could be recorded by them. The proposed operation of the European pharmacovigilance database that would allow this is described in the draft Commission guideline ENTR-6101-02 which is available on the EU Commission website www.pharmacos/eudra.org.

5.11.5 Access to EMEA database

Article 11(1) of the Directive restricts access to the European database to the competent authorities of the EEA States, the European Medicines Evaluation Agency (the Agency) and the European Commission.

5.11.6 Clinical trials in third countries

Regulation 33 proposes that if a sponsor conducts a clinical trial at sites in a third country i.e. a country outside the EEA, in addition to sites in the UK they would have to ensure that all SUSARs at that site and which are notified to him are entered into the European database described above.

5.11.7 Annual list of suspected serious adverse reactions and safety report

Under Regulation 34 a sponsor would have to provide the LA and the relevant ethics committee in a specified period with a list of all suspected serious adverse reactions in relation to each investigational medicinal product tested at sites in the UK and elsewhere which had occurred during the reporting year for which he were the sponsor. The reporting year would be the year ending on the anniversary of either the first date that the LA authorised the sponsor to conduct any clinical trial with that medicinal product in the UK or if the sponsor was conducting trials at sites in the UK and in an EEA State the first date that a trial with that product was first authorised in the EEA.

5.11.8 Offences relating to pharmacovigilance

Whilst a holder of a Clinical Trial Certificate (CTC) or an exemption was obliged to report serious adverse reactions, failure to comply was not a criminal offence under the Medicines Act. However, under Regulation 48 (g) any person who fails to comply with Regulations 31 to 34 described above would be guilty of a criminal offence. These offences have been proposed because failure to report SUSARs would cause a serious risk to participants in clinical trials.

5.12 General Provisions

The first paragraph of Article 19 of the Directive provides that the sponsor or a legal representative of the sponsor must be established in the Community. The second paragraph of the Article also provides that unless Member States have established precise conditions for exceptional circumstances, investigational medicinal products and the devices used for their administration shall be made available free of charge to the subject.

The provisions of Regulation 11, see in particular paragraphs (1) and (3), would implement the requirement in the first paragraph of Article 19. No person would be able to start or conduct a clinical trial in the United Kingdom unless the sponsor of the trial, or a person authorised to act on their behalf in relation to that trial, was established in the Community.

In relation to the second paragraph of Article 19, Regulation 26(3) of the draft (good clinical practice and the protection of clinical trial subjects) provides that the sponsor of a clinical trial must ensure that the products used in the trial and any devices used for the administration of those products are made available free of charge to the subjects of the trial. This would however be subject to paragraph (4), which provides that the restriction on charging does not apply to any charges which are made under

legislation imposing charges for the provision of goods or services as part of the NHS (for example, prescription charges). Such charges would therefore continue to be made and recovered from trial subjects.

5.13 Appeal procedures

5.13.1 Regulatory appeal to the appropriate committee

Regulation 25 proposes that if the LA has notified the sponsor that:

- there are grounds for not accepting a request for authorisation or
- the trial is authorised subject to specified conditions, or
- they do not accept a proposed modified or adapted amendment to the clinical trial authorisation, or
- they accept such an amendment subject to conditions, or
- they intend to amend the clinical trial authorisation as described above, or
- they must suspend or terminate the clinical trial,

the sponsor may give notice to the licensing authority of their wish to make written or oral representations to the appropriate committee (in practice the Committee on Safety of Medicines (CSM)) or if there is no such committee to the Medicines Commission as described below. However if a notice of suspension or termination is referred to an appropriate committee or the Medicines Commission it would remain in force unless revoked in accordance with Schedule 3 (see Regulation 29(9)). The sponsor would have to give their notice within a period of 28 days of the notification by the LA or such extended period as the LA may in any particular case allow. Schedule 3 of the Regulations would regulate the procedure for reference to the appropriate committee. It proposes that after hearing the written or oral representations the committee would report its findings and advise the LA. The LA would then, after considering the advice of the committee either confirm or alter its decision.

5.13.2 Appeal to the Medicines Commission

Schedule 3 paragraph 2(1) proposes that if a person that receives a notice from the LA as part of the procedures described above and he has not made representations to the Medicines Commission he may give notice to the LA within 28 days of receiving the notice (or such extended period as the LA may allow) of his wish to make written or oral representations to the Medicines Commission. The LA would then have to take into account the report and advice of the Medicines Commission and decide whether to confirm or alter its decision.

5.13.3 Appeal to the licensing authority or a person appointed by it

When after the above procedure the LA sends a notice to the sponsor, they could within the time allowed in the notice give notice of their wish to appear before and be heard by a person appointed for the purpose by the licensing authority or of making written representations to the licensing authority. The person appointed would not be a servant or officer of any Ministers that are part of the LA. If the sponsor requests, the hearing could be held in public and they could receive a copy of the report of the person appointed. The LA would then have to take into account the report and decide whether to confirm or alter their decision.

5.14 Enforcement and related provisions

5.14.1 Enforcement

The draft Regulation 48 contains provisions to make certain breaches a criminal offence. This is in line with medicines law that currently applies in the UK.

Under sections 108 to 110 of the Medicines Act 1968, the Secretary of State for Health (in relation to England), the National Assembly for Wales (in relation to Wales), the Scottish Ministers (in relation to Scotland), and the Department for Health, Social Services and Public Safety (in relation to Northern Ireland) each have a responsibility for enforcement of the provisions of the Act. In Scotland and Wales, however, this responsibility is exercised by the Medicines Control Agency acting under agency arrangements with the relevant administrations. For the purpose of enforcement, the Secretary of State, acting as an enforcement authority under section 108, duly authorises MCA officers to exercise the powers of entry, inspection and seizure in section 111 to 114 of the Act. These include rights to enter premises to inspect and take copies of documents, to take samples, to require the production of books and documents and to seize such goods and documents. Regulation 46 of the draft Regulations would apply those provisions for the purposes of the Regulations, subject to the various modifications set out in Schedule 7. The effect is that MCA officers authorised under the Act would be able to exercise the powers of entry, inspection and seizure for the purpose of enforcing compliance with the Regulations relating to clinical trials, including the provisions relating to compliance with good clinical practice and good manufacturing practice.

Regulation 49 would introduce new offences to deal with the submission of false or misleading information in respect of a clinical trial authorisation or a manufacturing authorisation. In particular, it makes it an offence to provide false or misleading information in the course of an application for an ethics committee opinion, a request for authorisation to conduct a clinical trial or an application for the grant of a manufacturing authorisation (paragraph 49(1)). In addition it would be a criminal offence for a sponsor, investigator, contract research organisation or other person involved in the conduct of a trial, or a person who holds a manufacturing authorisation, to provide false or misleading information to the MCA or an ethics committee.

The offences would not apply to all false or misleading information. They would only apply to "relevant information" - i.e. any information which is relevant to assessing the safety, quality or efficacy of an IMP, the safety or scientific validity of a clinical trial, or whether the conditions and principles of GCP are being complied with in relation to a trial.

Penalties for any person found guilty of offences under Clinical Trials Regulations are to be commensurate with those set out in the Medicines Act and associated Orders (Regulation 51). It is proposed that all the offences would be triable in a magistrate's court or the Crown Court. A conviction in a magistrates' court would lead to a fine not exceeding the statutory maximum (£5,000) or a term of imprisonment not

exceeding 3 months and conviction in the Crown Court would lead to a fine or imprisonment for a term not exceeding 2 years or both.

Most of the offences created under the draft Regulations would be "strict liability" offences. Regulation 50, however, would provide a defence of "due diligence". Under this provision it would be a defence for any person charged with an offence under the Regulations to prove that he took all reasonable cautions and exercised all due diligence to avoid the commission of the offence in question.

5.14.2 Infringement notices

In all cases where the MCA has concerns that there is a breach of the provisions of the Regulations, for example failure to comply with GCP, or conducting a trial otherwise than in accordance with the clinical trial authorisation, the MCA may issue an infringement notice (Regulation 47 (1)).

The infringement notice would inform the person on whom it is served (whether the sponsor, investigator or other individual) the grounds for considering that a contravention has occurred, (specifying the relevant provisions of the Regulations), the measures to be taken, to ensure that the breach does not continue or, does not recur, the time in which those measure must be taken and warning that unless the measures are met further action may be taken (see Regulation 47 (1)).

Where a person fails to comply with an infringement notice, then the licensing authority may suspend or revoke the clinical trial in accordance with Regulation 29(1). If an infringement notice is breached, the original breach of the Regulations is still itself a criminal offence and the licensing authority would be able to move directly to prosecution.

6 Fees

6.1.1 Fees for clinical trial applications

MCA proposes to charge fees for assessment of pharmaceutical, pre-clinical and medical data for all types of trials. The fees would reflect the time and resources required to complete the assessments. The table below shows the proposed levels of fee for each type of application. In addition MCA proposes to charge an annual service fee to provide for administrative activities and enquiries related to each programme of authorised trials with an investigational medicinal product.

6.1.2 Fees for academic trials

The Directive requires the UK to subject all clinical trials to an authorisation procedure, and does not distinguish between commercial or non-commercial trials. The MCA would assess requests for authorisation to conduct a clinical trial submitted by a sponsor; as with other medicines licence applications, it is proposed that the cost of such activities would be met by charging fees to the applicant for authorisation (i.e. the sponsor of the trial).

Proposed fees for clinical trial authorisations in 2004/2005

Category of Application	Proposed Fee for 2004/05 £
Phase I ³ initial application	610
Phase II ⁴ & III ⁵ initial	2700
application unknown IMP*	
Phase II & III initial	2250
application known IMP	
Phase IV ⁶ initial application ⁷	140
Additional Clinical Trial	100
Protocol Authorisation	
Other Amendments to IMP	100
dossier	
Annual service charge per	200
initial application	

The MCA are now considering the level of fees to be charged in relation to particular types of applications; and as part of our consultation on the proposed new Regulations we would invite comments on our proposed fees. Generally speaking, the fees charged for assessing an application is set by reference to the normal cost of the assessment work involved in dealing with the type of application in question. The MCA are, however, also considering the potential impact of fees on the individuals and organisations sponsoring different types of clinical trials; and in particular, those clinical trials which are conducted in an academic environment and without direct support from the pharmaceutical industry ("non-commercial trials"). In considering these points we would welcome your assistance in providing any information or evidence which may be relevant in considering the impact on such trials.

6.1.3 Fees related to IMP Manufacturing Authorisations

A specific application form for a new IMP manufacturing authorisation will be developed and it is proposed to charge the same fee as the current application fee for a manufacturing authorisation. Fees for a manufacturer's licence are currently payable under the Medicines (Products for Human Use-Fees) Regulations 1995 (S.I.

³ Phase I trials are pharmacokinetic trials conducted in healthy volunteers usually and currently not regulated by the Medicines Act 1968

⁴ Phase II trials are exploratory trials usually conducted in small groups of patients
⁵ Phase III trials are the appendic confirmatory trials usually conducted in large

⁵ Phase III trials are therapeutic confirmatory trials usually conducted in large numbers of patients

^{*} IMP = Investigational Medicinal Product

⁶ Phase IV trials are trials with products that have a marketing authorisation usually with the objective of ascertaining some new aspect of efficacy or safety. This definition could include for example additional pharmacokinetic studies on a marketed product in healthy volunteers.

⁷ This would also include applications where MCA has been authorised to cross refer to another application for the same IMP.

1995/1116), as amended. This includes the licence application, licence variations and inspections, plus an annual service charge during the currency of a licence.

Manufacturing facilities for IMPs are not currently inspected and so an inspection programme would need to be initiated.

Currently the fee for the inspection of a manufacturer is based upon the size of the company inspected, determined by the number of relevant employees. It is proposed to use the same principle for inspection of IMP manufacturers. MCA proposes to introduce an inspection fee from the date these Regulations come into force, for manufacturers of investigational medicinal products, based on the size and complexity of the manufacturing operation.

6.1.4 Fees for GCP inspections

Inspection fees would be levied for GCP inspections which are to commence in May 2004. The fee arrangements and structure for GCP inspections are still to be finalised. Inspection charges for GCP inspections would be consulted on as part of the consultation exercise for the MCA fees amendments to be introduced in 2004.

6.1.5 Fees for ethics committee opinion

Fee arrangements for applications for ethics committee opinion under these Regulations are under review and may be the subject of separate consultation in 2003, with a view to any specific Regulations being introduced in time for the commencement of the scheme on 1 May 2004.

7 Transitional arrangements

7.1.1 Current exemptions and certificates

When these Regulations come into force on 1 May 2004 there would no longer be any exemptions from holding a clinical trial authorisation. Therefore holders of Clinical Trial Certificates (CTCs), Clinical Trial Exemptions (CTXs) Clinical Trial of a Market Product (CTMPs) and Doctors and Dentists Exemptions (DDXs) for trials that fall within the definition of a clinical trial under the Directive would have to obtain a Clinical Trial Authorisation (CTA). Since CTCs and CTXs are assessed to the same standards as a CTA for quality and safety, it is proposed to convert those that were granted before these Regulations come into force to CTAs from 1 May 2004 without a fee. However, some investigators conducting trials with a DDX granted before these Regulations come into force would have to identify a sponsor that would apply for a CTA before 1 May 2004 if the trial is to continue after that date.

7.1.2 New applications and renewals

Sponsors who would apply for a new CTC, CTX, DDX or CTMP between the date these Regulations come into force and 1 May 2004 would be encouraged to apply for

a CTA including payment of the fee. The effect of granting the authorisation application would be that—

- (a) prior to May 2004 they would be exempt from the requirements to obtain a CTC or CTX in order to conduct the trial, and
- (b) from 1st May 2004 it would become a full authorisation for the purposes of the Regulations.

Alternatively, under the legislation sponsors and investigators would be allowed to apply for an exemption to run until 30 April 2004 and then to apply for a CTA to run from 1 May 2004 onwards. Further, those conducting studies in healthy volunteers that are not regulated by the Medicines Act would require a clinical trial authorisation from 1 May 2004.

8. Comments

8.1 Invitation to comment

8.1.1 Consultation letter

We welcome comments on all aspects of the proposed Regulations which are outlined in this document.

8.1.2 Regulatory impact assessment

You are also invited to comment on the draft Regulatory Impact Assessment (RIA), which is attached at Annex C.

8.1.3 Publication of comments

To help informed debate on the issues raised by this consultation exercise, and within the terms of the Code of Practice on Access to Government Information, the Agency intends to make publicly available responses received to this consultation. Copies will be available after the public consultation has concluded. It will be assumed that your comments can be made publicly available in this way unless you indicate that you wish your response to be treated as confidential and excluded from this arrangement.

Should you have any questions regarding the proposed Regulations, please contact Matthew Garland, MCA European Support Unit Tel: 0207 273 0401. This document will be posted to the websites of the MCA and the Department of Health. Further copies are available on request. If you consider there are other organisations that should be invited to comment on these proposals, please contact Matthew Garland at the MCA and we will arrange for a consultation pack to be sent.

Medicines Control Agency February 2003