DESCRIPTION OF THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004

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INTRODUCTION

The Medicines for Human Use (Clinical Trials) Regulations 2004 (the Regulations) regulate clinical trials in the UK since they came into force on the 1 May 2004. They replace the current clinical trial provisions of the Medicines Act 1968 and its secondary legislation and will transpose Directive 2001/20/EC[1] into UK law.

The Directive requires the "competent authorities" of the Member States to perform certain functions in relation to clinical trials. The UK competent authority responsible for those functions is the "licensing authority". The licensing authority was established under the Medicines Act 1968; it consists of Ministers who act through The Medicines and Healthcare products Regulatory Agency (MHRA). To help to clarify how the Regulations will operate in practice, the descriptions of the Regulations below refer to the MHRA in some places rather than the licensing authority, as stated in the Regulations. MHRA's website www.mhra.gov.uk acts as a gateway to additional information and guidance on implementing the Regulations including access to the Regulations themselves.

The following sections provide an executive summary of the changes to UK clinical trials practice and legislation, a summary of some of the benefits to public health and a short description of each of the Regulations. The first two sections cross-refer to the descriptions of the Regulations in the third section. This description does not change the regulations in any way but aims to help those involved in the conduct of clinical trials to follow and understand the regulations.

EXECUTIVE SUMMARY

Most of the provisions of the Directive and guidance are in line with current clinical trial practice in the UK. The major changes to current UK practice are that:

- Pharmacology studies in healthy human volunteers (Phase 1 studies) require authorisation from the MHRA where previously they only needed a favourable opinion of an ethics committee;
- Investigational medicinal products (IMPs) must be manufactured to good manufacturing practice (GMP) standards and the manufacturer must have a manufacturing licence; and
- Each trial must have an identified sponsor who takes responsibility for its initiation, management and conduct. The Regulations allow a group to collaborate to take on these responsibilities.

[1] 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

However, some other aspects of current UK practice regulated by guidance, were included in the Directive as legal requirements. Therefore the Regulations introduce the following new provisions:

- To establish our ethics committee system on a statutory basis (*Regulations 5 to 10, and Schedule 2*);
- To require all clinical trials to be conducted in accordance with the principles of good clinical practice (GCP) *(Regulations 28 to 31, and Schedules 1 and 5);*
- To provide additional protection for minors and physically or mentally incapacitated adults who are candidates for clinical trials *(Regulations 14 to16 and Parts 3 & 5 of Schedule 1 for incapacitated adults and Regulation 15 and Part 4 of Schedule 1 for minors)*;
- To require sponsors to provide trial medicines free of charge to patients if they are not covered by a prescription charge *(Regulation 28)*;
    - To provide for inspection by the MHRA for GCP and GMP to help ensure those standards are maintained *(Regulations 47 to 52, Parts 2 & 3 of Schedule7,and Schedule 9*; and
- To provide for enforcement of these new provisions *(Regulations 47 to 52 and Schedule 9)*.

PUBLIC HEALTH BENEFITS

This section discusses why some of the key changes are important to the protection of public health. This section cross-refers to the next section, which provides a brief description of each Regulation to which the references in the subsections below cross-refer.

Good clinical practice

The requirement to conduct all clinical trials in accordance with the internationally recognised principles of good clinical practice (GCP), will help to ensure that all UK trials are conducted to the appropriate high standard and that risks to patient volunteers are minimised. *(Regulations 2, 28, 29, 30 and Schedule 1)*

Good manufacturing practice

The requirement to manufacture investigational medicinal products to GMP standards will help ensure that trial participants are not exposed to poor quality or badly prepared medicines. (*Regulations 36-46 and Schedules 7 & 8)*

GCP and GMP inspections and enforcement

Inspections by the Medicines and Healthcare products Regulatory Agency (MHRA) to check that the principles and standards of GCP and GMP, are being followed will improve the overall quality of UK clinical trials and help identify non-compliance. And of course if misconduct persists or inspectors suspect fraud the regulations provide powers of enforcement. *(Regulations 47 to 52, Parts 2 & 3 of Schedule 7 and Schedule 9)*

Protection of incapacitated adults

The Regulations contain provisions for the protection of adults incapable of giving informed consent, for example, those with advanced Alzheimer's disease, who should be able to benefit from research that can improve their condition. However the

decision on whether to consent to, or refuse, participation in a trial will be taken by a "legal representative" who is independent of the research team and should act on the basis of the person's presumed wishes.

The Regulations include a cascade system by which:

— Informed consent is first sought from a person whose relationship to the person makes them suitable to act as their legal representative;
— If there is no such person or they are unwilling to take that responsibility, then it will be sought from the doctor primarily responsible for the person's treatment; or
— If he is involved in the conduct of the trial, or is not available or willing to take that responsibility, a person nominated by the relevant health care provider may give informed consent. The health care provider is prevented from nominating a person involved in the conduct of the trial

In the last situation a health service body might be expected to have a list of suitable nominated persons that can be called upon. The legal provisions for incapacitated adults in Scotland are slightly different. Except in cases of emergency treatment, the legal representative will be the person who is able to consent to treatment under the Adults with Incapacity (Scotland) Act 2000. *(Regulations 14 to16 and Parts 3 & 5 of Schedule 1).*

Protection of minors

The Regulations provide additional protection for a minor who is being considered for a clinical trial i.e. a person under the age of 16. The additional protection for minors comes at a time when we expect more children to be asked to participate in clinical trials, as part of an international initiative to provide medicines for children that are fully licensed. They require, among other provisions, that:

- an ethics committee considering the trial must receive advice on the relevant field of paediatric care; and
- a person with parental responsibility or a legal representative must give informed consent and may withdraw the young person at any time; and

In relation to the minor himself:

- staff with experience with young persons must inform him of the risks and benefits of the trial according to his capacity to understand;
- The investigator must consider his explicit wish to refuse to participate or to be withdrawn from the trial at any time;
- The clinical trial must relate directly to an illness from which he suffers or that can only be carried out on minors; and
- The trial must aim to provide some direct benefit for the group of patients involved.

(Regulation 15 and Part 4 of Schedule 1)

Pharmacovigilance arrangements

Investigators and trial sponsors together must record serious unexpected adverse reactions thought to be caused by the trial medicine and report them to the MHRA. Assessors at the MHRA can identify safety signals from these reports indicating when trial participants are at increased risk and the trial should be modified or stopped. *(Regulations 32-35)*.

The Directive also requires each of the 25 Member States to enter safety data from trials in their country into a single European pharmacovigilance database which will be a resource to the UK for early identification of safety signals derived from the clinical trials in a population of over 400 million people. *(Regulation 34)*

DETAILED DESCRIPTION OF THE REGULATIONS

PART 1: INTRODUCTORY PROVISIONS

Citation and commencement

Regulation 1 specifies the full title that people should use to refer to the Regulations and the date they come into force.

Interpretation

Regulation 2 provides a list of definitions of the words or terms used in the Regulations. 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). In particular, it defines "the conditions and principles of good clinical practice" as those conditions and principles specified in **Schedule 1** (see below under **regulation 28**).

Sponsor of a clinical trial

Regulation 3 provides the definition of a sponsor. It gives several options. One option is for a group of two or more persons responsible to allocate responsibility for carrying out the functions of a sponsor. One may be responsible for the sponsor's functions relating to obtaining authorisation; another for the conduct of the trial and the arrangements for ensuring compliance with good clinical practice; and another for pharmacovigilance (the reporting of adverse events).

Responsibility for functions under the Directive

Regulation 4 provides that the "licensing authority" is the UK competent authority in relation to clinical trials and that it shall perform those functions imposed by the Directive on the UK as a Member State. The licensing authority was established under the Medicines Act 1968; it consists of Ministers but acts by the Medicines and Healthcare products Regulatory Agency (MHRA).

PART 2: ETHICS COMMITTEES

United Kingdom Ethics Committees Authority

Regulation 5 establishes a United Kingdom Ethics Committees Authority (the Authority) which is responsible for establishing, recognising and monitoring those ethics committees which give opinions on clinical trials on medicines under the Regulations. The Authority consists of the Secretary of State for Health, the National Assembly for Wales, the Scottish Ministers and the Department for Health, Social Services and Public Safety in Northern Ireland. The regulations specify how the Authority may carry out its functions.

Establishment of ethics committees

Regulation 6 provides the Authority with the powers to establish or abolish an ethics committee, set the classes of clinical trials it may consider, and the area for which it may act.

Recognition of ethics committees

Regulation 7 provides the Authority with the powers to recognise an ethics committee and specifies how a new ethics committee may apply for recognition. It also provides the Authority with powers to recognise existing NHS ethics committees without an application, and to vary or revoke the conditions of a committee's recognition.

Revocation of recognition

Regulation 8 provides the Authority with powers to revoke a recognition of an ethics committee and specifies the criteria that it uses to revoke a recognition.

Constitution and operation of ethics committees

Regulation 9 brings into force the additional provisions relating to ethics committees in **Schedule 2**. These provisions provide for: the restrictions on membership of ethics committees; arrangements for chairmen and deputy and co-opted members; rules relating to the procedures of ethics committee meetings; provision for funding, staffing, premises and annual reports; and the transfer of business from committees that are being abolished or which cease to exist or be recognised by the Authority.

Other functions of the Authority

Regulation 10 requires the Authority to monitor the performance of UK ethics committees and allows it to advise ethics committees on their performance and assist them.

PART 3: AUTHORISATION FOR CLINICAL TRIALS AND ETHICS COMMITTEE OPINION

Interpretation of Part 3

Regulation 11 provides additional definitions of terms relating to amendments to the clinical trial authorisation.

Requirement for authorisation and ethics committee opinion

Regulation 12 prohibits anyone from commencing or conducting a clinical trial, recruiting subjects or advertising to recruit subjects to be in a trial unless certain conditions are met. In particular, a trial may only be started or conducted if it has been authorised by the MHRA and has been given a favourable opinion by an ethics committee.

Supply of investigational medicinal products for the purpose of clinical trials

Regulation 13 prohibits anyone from selling or supplying an investigational medicinal product (IMP), i.e. a medicinal product to be used or tested in a clinical trial (or a placebo), to those involved in a clinical trial unless certain conditions are met. In particular, the trial must be authorised by the MHRA and products without a UK valid marketing authorisation which are made abroad have to meet certain quality

testing requirements. Products manufactured or imported prior to 1 May 2004 and products sold or supplied in accordance with a marketing authorisation in the UK are exempt from some or all of these conditions.

Application for ethics committee opinion

Regulation 14 sets out the procedures a chief investigator must follow to obtain an ethics committee opinion and the particular procedures that he must follow to obtain an ethics committee opinion in Scotland or for a clinical trial involving medicinal products for gene therapy. **Part 1 of Schedule 3** sets out the particulars and documents that an applicant must submit with an application for an ethics committee opinion.

Ethics committee opinion

Regulation 15 sets out how an ethics committee must consider an application for such an opinion. In particular it specifies the time within which an ethics committee must give its opinion (which is different for different types of product). It also specifies the matters an ethics committee must consider in preparing its opinion, including arrangements for obtaining informed consent for minors or adults incapable of giving such consent by reason of physical or mental incapacity. It further requires an ethics committee to give an opinion on any other matter that it considers relevant and to publish summaries of its opinions.

Review and appeal relating to ethics committee opinion

Regulation 16 sets out the procedure by which a chief investigator may appeal against an unfavourable opinion of an ethics committee. Provision is also made for an applicant to require the Gene Therapy Advisory Committee to review its opinion in relation to a gene therapy trial It also introduces **Schedule 4,** which regulates the procedure that must be followed when a chief investigator wishes to appeal against an unfavourable opinion.

Request for authorisation to conduct a clinical trial

Regulation 17 sets out the procedure that a sponsor must follow to make a request to the competent authority for authorisation to conduct a clinical trial. **Part 2 of Schedule 3** specifies the information which must accompany such a request. **Regulations 18, 19 and 20** then govern the authorisation procedure for different types of trial.

Authorisation procedure for clinical trials involving general medicinal products

Regulation 18 governs the authorisation procedure for clinical trials involving general medicinal products (i.e. all those not covered by regulations 19 and 20). It sets out the procedures for the MHRA to consider and respond to the request and the time within which it must make that response. In essence, the MHRA have 30 days in which to object to the trial, otherwise it is treated as authorised. It further provides the procedure by which a sponsor may respond to any grounds the competent authority has for not accepting the request.

Authorisation procedure for clinical trials involving medicinal products for gene therapy etc.

Regulation 19 governs the authorisation procedure for clinical trials involving medicinal products for gene therapy and somatic cell therapy or medicinal products

containing genetically modified organisms. Such trials require a written authorisation from the MHRA. The authority has 30 days to either issue a written authorisation or a notice refusing authorisation. The time period is extended to 90 days if an expert committee is consulted. If refused, the sponsor may submit an amended request.

Authorisation procedure for clinical trials involving medicinal products with special characteristics

Regulation 20 governs the authorisation procedure for clinical trials involving medicinal products which are "high technology" products subject to licensing by the European Medicines Agency, biological medicinal products or other medicinal products which have 'special characteristics'. Such trials require written authorisation from the MHRA. The MHRA has 30 days to issue an authorisation or a notice refusing authorisation. If refused, the sponsor may submit an amended request.

Clinical trials conducted in third countries

Regulation 21 provides the licensing authority with the power to require the sponsor to provide undertakings that permit the MHRA to inspect the sponsor's premises, or premises where the trial will be conducted in that country, for compliance with good clinical practice (GCP) and makes failure to do so grounds for refusing a request for authorisation.

Amendments to clinical trial authorisation

Regulation 22 allows the MHRA and the sponsor to amend a clinical trial authorisation in accordance with the procedures in **regulations 23 to 25.**

Amendments by the licensing authority

Regulation 23 sets out the criteria that the MHRA must consider before amending a clinical trial authorisation and the procedure for making the amendment including the requirement for the MHRA to inform the sponsor of its intention, the reason for the amendment and the option for the sponsor to respond to the notice of amendment and the need for the MHRA to consider that response before deciding whether to make the amendment.

Amendments by the sponsor

Regulation 24 allows a sponsor to make "non-substantial amendments" at any time and sets out the procedure for notifying a "substantial amendment" to the MHRA and/or the relevant ethics committee. It further sets out the time by which the MHRA must decide whether to allow the sponsor to make the amendment and by which the ethics committee must provide its opinion. **Part 3 of Schedule 3** provides the particulars that must accompany a valid notice of amendment. **Regulation 11**, sets out what constitutes a "substantial amendment".

Modifying or adapting rejected proposals for amendment

Regulation 25 allows the sponsor to modify or adapt a proposed amendment for which an ethics committee has given an unfavourable opinion or which the MHRA has refused. It further provides the time within which the MHRA and/or the relevant ethics committee must respond to a notice of a modified or adapted amendment, and enables the sponsor to make such an amendment if it is not refused or rejected.

Reference to the appropriate committee or the Medicines Commission

Regulation 26 provides the sponsor with the right to appeal against an unfavourable ethics committee opinion, a refusal by the MHRA or the imposition of conditions on authorisation by the authority. The appeal consists of a right to make representations to the "appropriate committee" (i.e. the Committee on Safety of Medicines). **Schedule 5** provides for the procedure where representations are made to committee. If the sponsor is dissatisfied with the committee's advice, they may make further representations to the Medicines Commission; and subsequently to a person appointed by licensing authority.

Conclusion of clinical trial

Regulation 27 requires the sponsor to notify the MHRA and the relevant ethics committee in writing that the trial has ended and sets the time by which the sponsor must inform the MHRA and relevant ethics committee. **Part 4 of Schedule 3** sets out the particulars that the sponsor must provide in notification of the end of a trial.

PART 4: GOOD CLINICAL PRACTICE AND THE CONDUCT OF CLINICAL TRIALS

Good clinical practice and protection of clinical trial subjects

Regulation 28 prohibits anyone from conducting a clinical trial or performing the duties of a sponsor unless they adhere to the conditions and principles of good clinical practice. The conditions and principles are set out in **Schedule 1**.

Schedule 1 sets out the conditions and principles that apply in the case of all trials (Part 2), those that apply only to trials of adults able to consent or who have given prior consent (Part 3), those that apply to trial involving children (Part 4) and those that apply to trials involving incapacitated adults (Part 5). The Schedule includes the requirements relating to informed consent, for "legal representatives" to give consent on behalf of incapacitated adults, for the provision of information to participants and the right to withdraw.

Regulation 28 also requires the sponsor to ensure that investigational medicinal products, and devices to administer them, are provided to the subject free of charge except for prescription and other NHS charges. It also allows the sponsor to delegate responsibility for performing duties under this regulation to another person at a specific site in a multicentre trial.

Conduct of trial in accordance with clinical trial authorisation etc.

Regulation 29 prohibits anyone from conducting a clinical trial other than in accordance with the clinical trial protocol, the terms of the request for authorisation, the application for ethics committee opinion and any documents accompanying the request or application as well as any condition imposed by the licensing authority.

Urgent safety measures

Regulation 30 allows the sponsor and investigator to take appropriate safety measures to protect trial subjects against any immediate hazard to their health or safety. It further sets the time by which the sponsor must inform the MHRA and ethics committee of the measures taken and explain the need for them.

Suspension or termination of clinical trial

Regulation 31 provides powers to the MHRA to suspend or terminate a clinical trial when it considers that the conditions of authorisation are not being met or it has concerns about the safe conduct or scientific validity of a trial (either generally or at a specific trial site). It further, sets out the procedure for terminating or suspending a trial, including the requirement to inform the sponsor of the authority's intention one week before they take the action. The requirement for prior notification does not apply where there is an imminent risk to the health or safety of the trial participants. The regulation also allows the person on whom the termination or suspension notice is served to make written or oral representations to the Committee on Safety of Medicines (and then the Medicines Commission) in accordance with the procedures set out in **Schedule 5**.

PART 5: PHARMACOVIGILANCE

Notification of adverse events

Regulation 32 requires the investigator to report all serious adverse events to the sponsor immediately except those identified in the protocol or investigator's brochure as not requiring immediate reporting. It also requires the investigator to provide a detailed written report on the event within the time periods specified in the protocol; and any additional information requested by the sponsor or ethics committee in cases that results in the death of a subject. It also requires that subjects must be identified by means of a number.

Notification of suspected unexpected serious adverse reactions (SUSAR)

Regulation 33 requires the sponsor to report to the MHRA, and to competent authorities of any state in the European Economic Area (EEA State) where the trial is being conducted, any suspected unexpected serious adverse reaction (SUSAR) which is fatal or life-threatening within specified time periods. Other SUSARs must be reported, but with longer time periods for doing so. The sponsor may fulfil his obligation to report to the MHRA, or the competent authority of another EEA State, by entering the information into the European pharmacovigilance database established by Article 11 of the Directive. In addition, the regulation requires the sponsor to inform investigators, working on clinical trials involving a particular product, of any SUSAR relating to that product which occurs in a trial for which the sponsor is responsible. It also requires the MHRA to keep a record of all SUSARs that are brought to its attention and ensure that the sponsor or the MHRA enters the details of those SUSARs into the European phamacovigilance database.

Clinical trials conducted in third countries

Regulation 34 requires the sponsor to enter information on SUSARs into the European pharmacovigilance database when they occur at a site in a country outside the EEA in a clinical trial that is also being conducted in the UK.

Annual list of suspected serious adverse reactions and safety report

Regulation 35 requires the sponsor to provide the MHRA and the relevant ethics committee with an annual list of suspected serious adverse reactions (SSARs) which have occurred within the "reporting year", which it defines according to whether the product being used has a marketing authorisation. It specifies that the annual list must

include all SSARs occurring in the period in trials in the UK or elsewhere and in trials with the same product conducted in trials outside the UK for which the sponsor is responsible. It further requires the sponsor to provide a report on the safety of the subjects in those trials.

PART 6: MANUFACTURE AND IMPORTATION OF INVESTIGATIONAL MEDICINAL PRODUCTS

Requirement for authorisation to manufacture or import investigational medicinal products

Regulation 36 prohibits the manufacture, assembly or import of an investigational medicinal product other than in accordance with a manufacturing authorisation granted for the purpose, unless the product has a marketing authorisation.

Exemption for hospitals and health centres

Regulation 37 provides an exemption from the need for a hospital or health centre to hold a manufacturing authorisation to assemble an investigational medicinal product in a hospital or health centre, when the "assembly" is carried out by a doctor or pharmacist, or under the supervision of a pharmacist. "Assembly" is related to packaging and labelling, and not to the preparation of medicines from their ingredients. The exemption applies only if the product is to be used exclusively in that hospital or health centre or any other that is a trial site for the clinical trial in which the product is to be used.

Application for manufacturing authorisation

Regulation 38 sets out how to apply for a manufacturing authorisation and provides that the application must be accompanied by information specified in **Schedule 6** and any fee which may be payable.

Consideration of application for manufacturing authorisation

Regulation 39 sets the time period within which the MHRA must respond to an application for a manufacturing authorisation and allows the licensing to ask the applicant for additional information. It further allows the MHRA to request undertakings, by the manufacturer of products which the applicant intends to import from a country other than an EEA State, to permit the MHRA to inspect the premises where the products are manufactured and the operations carried out in the manufacture.

Grant or refusal of manufacturing authorisation

Regulation 40 sets out the conditions that must be met if the MHRA is to grant a manufacturing authorisation. It also specifies what activities are authorised by such an authorisation. The MHRA is given the power to specify the provisions of the authorisation, including the standard provisions set out in **Schedule 7**. **Part 2 of Schedule 7** specifies the standard provisions that apply to authorisations for the manufacture and assembly and Part **3 of Schedule 7** specifies the standard provisions that apply to authorisation for importation

Regulation 40 also specifies that the procedure in **Schedule 8** must be followed where the MHRA propose to refuse an application or grant it otherwise than in accordance

with the application. The applicant has a right to a hearing before a person appointed by the licensing authority.

Application and effect of manufacturing authorisation

Regulation 41 provides that the manufacturing authorisation applies only to the descriptions of investigational medicinal products, the operations and the premises specified in the application.

Obligations of a manufacturing authorisation holder

Regulation 42 requires the holder to comply with the principles and guidelines of good manufacturing practice and any provisions that the licensing authority incorporated in the authorisation as a condition of granting it (for example, the standard provisions specified in Schedule 7).

Qualified persons

Regulation 43 requires the manufacturing authorisation holder to have the services of a "qualified person" at his disposal. The qualifications and experience necessary to act as a qualified person are set out in the definition of "qualified person" in **Regulation 2**. Regulation 43 sets out the duties of a qualified person (by reference to the Clinical Trials Directive) and how he must carry them out. In particular he must check production batches of manufactured products and certify that they are of a satisfactory quality. It provides powers to the licensing authority to prohibit a manufacturing authorisation holder from using the services of any qualified person that in the authority's opinion does not satisfy criteria of qualifications and experience or is not carrying out his duties adequately. In this case, it requires the licensing authority to provide the holder of the manufacturing authorisation and the qualified person the opportunity to make representations to the licensing authority orally or in writing.

Variation of manufacturing authorisation

Regulation 44 provides powers to the licensing authority to vary a manufacturing authorisation in accordance with an application or otherwise. It also requires the MHRA to consider a valid application to vary a manufacturing authorisation made by its holder. It further sets out the time within which the MHRA may vary or refuse to vary an authorisation following an application, allowing a longer period where the MHRA decides to make an inspection.

In addition it allows the MHRA to request additional information from the applicant and to suspend the above time period until the MHRA receives that information. It also provides that the provisions of **Schedule 8** will apply when the MHRA proposes to vary a manufacturing authorisation without receiving an application from the holder of the authorisation; this gives the applicant a right to make representations to a person appointed by the licensing authority. It also requires the MHRA to notify a manufacturing authorisation holder in writing, giving its reasons, when it varies his authorisation without receiving an application or when it refuses to vary his authorisation in accordance with an application.

Suspension and revocation of manufacturing authorisation

Regulation 45 gives powers to the licensing authority to suspend or revoke a manufacturing authorisation and sets out the grounds on which it may do so. It also allows the licensing authority to suspend or revoke a manufacturing authorisation

totally or to limit it to certain types or batches of investigational medicinal products. It provides that the provisions of **Schedule 8** will apply where the licensing authority revokes or suspends a manufacturing authorisation (i.e. an authorisation holder has a right to make representations to a person appointed by the licensing authority) and that it will notify the holder in writing, giving the reasons.

PART 7: LABELLING OF INVESTIGATIONAL MEDICINAL PRODUCTS

Labelling

Regulation 46 requires investigational medicinal products to be labelled in accordance with the requirements of the Commission Directive on good manufacturing practice as they relate to labelling of investigational products, including the information that must be included on the label. In particular, the labelling must ensure protection of the trial subject, enable identification of the product and trial and assist proper use of the product. The regulation also provides an exemption from these requirements for products with a marketing authorisation, if they are prescribed by a doctor, dentist or pharmacist/nurse prescriber, labelled in accordance with the existing UK requirements for medicines dispensed by pharmacists, and are to be used in a clinical trial on patients for which the product is indicated in that authorisation.

PART 8: ENFORCEMENT AND RELATED PROVISIONS

Application of enforcement provisions of the Act

Regulation 47 provides that certain enforcement provisions of the Medicines Act 1968 apply for the purposes of these regulations. The effect is to require "enforcement authorities" to enforce the provisions of the Regulations and to confer powers to enter premises, conduct inspections, seize documents and take and test samples. The enforcement authorities are the Secretary of State for Health (for England), Scottish Ministers (for Scotland), the National Assembly for Wales (for Wales) and the Department for Health, Social Services and Public Safety (for Northern Ireland). The authorities for England, Wales and Scotland in practice act by the Medicines and Healthcare products Regulatory Agency and its staff.

Infringement notices

Regulation 48 gives powers to an enforcement authority to serve a notice in writing - an "infringement notice" - on a person they consider has contravened any provision to which this regulation applies. This Regulation applies to the regulations concerning the conduct of clinical trials (including compliance with GCP, urgent safety measures and amendments to authorisation) and the reporting of adverse events. It also sets out the information, directions and warnings that the enforcement authority must or may include in the infringement notice. It also requires the enforcement authority to immediately inform the competent authorities of each EEA State in which the relevant trial is being conducted, the relevant ethics committee in the UK and the European Commission.

Offences

Regulation 49 makes it a criminal offence for a person to contravene certain regulations which it specifies. The list of provisions covers the obligations on sponsors, investigators and others involved in the conduct of the clinical trial. In addition it describes certain other activities that constitute an offence (e.g. failure to comply with a suspension notice; supplying a product for the purposes of a clinical trial knowing that it is not properly labelled).

False or misleading information

Regulation 50 makes it a criminal offence for a person to provide false or misleading information in an application for an ethics committee opinion, for a clinical trial authorisation and for a manufacturing authorisation. It also makes it an offence for a person who is conducting a clinical trial, is a sponsor or acting under arrangements made with a sponsor, or is the holder of a manufacturing authorisation, to provide the MHRA or an ethics committee any "relevant information" (which it defines) that is false or misleading. It further makes it an offence for a "qualified person" to provide the MHRA or a manufacturing authorisation holder with false or misleading information.

Defence of due diligence

Regulation 51 provides that a person who took all reasonable precautions and exercised all due diligence to avoid the commission of an offence shall be deemed not to have committed an offence under these Regulations unless a prosecution proves beyond reasonable doubt to a court or jury that the defence of due diligence is not sufficient.

Penalties

Regulation 52 sets out the penalties that may be applied when a person is found guilty. The maximum penalty on conviction in the magistrates' court is a fine of £5,000 or a prison sentence of 3 months. The maximum penalty on conviction in the Crown Court is a prison sentence of 2 years (and a fine).

PART 9: MISCELLANEOUS PROVISIONS

Construction of references to specified publications

Regulation 53 specifies that references in authorisations granted under the Regulations to certain publications specified in section 103 of the Medicines Act (including the European and British Pharmacopoeias and the British National Formulary) are to be interpreted as reference to the latest editions

Consequential and other amendments to enactments

Regulation 54 provides for the amendment of the provisions of the enactments specified in **Schedule 10**. This includes amendments to the Medicines Act 1968 (in particular to amend the provisions relating to clinical trials), the Adults with Incapacity (Scotland) Act 2000 and a number of regulations and orders which refer to clinical trials and ethics committees.

Revocations

Regulation 55 revokes the enactments specified in column (1) of **Schedule 11** to the extent specified in column (3) of that Schedule. In particular, the regulations and orders regulating clinical trials under the Medicines Act 1968 are revoked.

Transitional provisions

Regulation 56 provides for transitional provisions set out in **Schedule 12**. In particular, paragraph 1 provides for cases where a trial has received ethical approval before 1st May 2004 (the date the Regulations come into force); in essence, if the committee that approved the trial is not recognised by the UKECA by 1st May 2006, responsibility for monitoring the trial must transfer to another recognised committee. Paragraph 2 concerns applications for an ethical opinion received but not determined before 1st May; they must be treated as applications under the Regulations. Paragraphs 3 to 6 concern trials granted clinical trial certificates or exemptions under the existing regime under the Medicines Act 1968 before 1st May 2004; those trials may continue as though authorised under the Regulations. Paragraph 7 concerns applications or notifications relating to such certificates or exemptions received but not determined before 1st May 2004; they are to be treated as requests for authorisation under the Regulations.

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