

EXPLANATORY MEMORANDUM TO
THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) AMENDMENT
REGULATIONS 2006

2006 No. 1928

1. This explanatory memorandum has been prepared by the Medicines and Healthcare products Regulatory Agency/Department of Health and is laid before Parliament by Command of Her Majesty.

1.1 This memorandum contains information for the Joint Committee on Statutory Instruments.

2. Description

2.1 These Regulations principally implement *Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products* (the GCP Directive) through amendment to the Medicines for Human Use (Clinical Trials) Regulations 2004 [S.I. 2004/1031] (the Clinical Trials Regulations).

In addition, these Regulations add a new provision to the Clinical Trials Regulations and amend two existing ones as well as correcting various minor errors.

3. Matters of special interest to the Joint Committee on Statutory Instruments

These Regulations correct errors previously reported by the JCSI in its 19th Report in connection with the Clinical Trials Regulations (2004/1031).

4. Legislative background

The Clinical Trials Directive (Directive 2001/20/EC) regulates clinical trials of medicines, including medicines under development, in humans across the European Community. The Clinical Trials Directive was implemented in the UK by the Clinical Trials Regulations on 1 May 2004.

The Clinical Trials Directive expressly stated that further detail would be provided in relation to certain aspects of clinical trial regulation. This resulted in the GCP Directive. Some aspects of the GCP Directive had been anticipated in the Clinical Trials Regulations because a draft of the Directive was available prior to the making of that instrument. The details of the GCP Directive that had not been anticipated are implemented by these Regulations. A transposition note is attached.

There is no scrutiny history for the GCP Directive. It was not subject to Parliamentary scrutiny as it is a technical Directive for the Clinical Trials Directive (2001/20/EC).

5. **Extent**

This instrument applies to all of the United Kingdom and Northern Ireland.

6. **European Convention on Human Rights**

The Secretary of State for Health has made the following statement regarding human rights:

In my view the provisions of the Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 are compatible with the Convention rights.

7. **Policy background**

Since 1 May 2004, clinical trials conducted in the European Union are regulated under the Clinical Trials Directive. The Clinical Trials Directive aims to harmonise the laws and administrative provisions of Member States in relation to the regulation of clinical trials on medicines. The Clinical Trials Directive requires that all clinical trials are designed, conducted and reported in accordance with good clinical practice. This is to ensure that the rights, safety and well-being of those participating in clinical trials are protected and that the results of those trials are credible. The Clinical Trials Directive also requires that the manufacture or import of medicines for use in clinical trials must be subject to the holding of an authorisation and that such products are manufactured in accordance with good manufacturing practice (to ensure the safety and quality of those products).

7.1 The GCP Directive adds detail to the Clinical Trials Directive. In particular, it makes provision for:

- the principles of good clinical practice for the design, conduct and reporting of clinical trials on human subjects involving medicines, as foreseen in Articles 1 (3) of the Clinical Trials Directive (Chapter 2, Articles 2-8);
- changes to the obligations of ethics committees, as foreseen in Article 6 of the Clinical Trials Directive (Chapter 2, Article 6), in particular in relation to document retention;
- new requirements on sponsors/investigators in relation to the investigator's brochure (a documents summarising the clinical and non-clinical data relevant to the trial) and retention and archiving of trial documentation, as foreseen in Article 6 of the Clinical Trials Directive (Chapter 2, Article 8);
- the requirements for authorising the manufacture or importation of medicines, as foreseen in Article 13 (1) of the Clinical Trials Directive (Chapter 3, Articles 9-15);
- the retention and archiving of trial documentation, as foreseen in Articles 15(5) of the Clinical Trials Directive (Chapter 4, Articles 16-19);
- the qualifications of inspectors, as foreseen in Articles 15(5) of the Clinical Trials Directive (Chapter 5, Articles 21-22); and
- inspection procedures, as foreseen by Article 15(5) of the Clinical Trials Directive (Chapter 6, Articles 23-30).

7.2 These Regulations implement the GCP Directive by amending the Clinical Trials Regulations so far as is necessary (some provisions of the GCP Directive were anticipated). UK stakeholders were informed that amendments to the Clinical Trials Regulations would be necessary to implement the GCP Directive when the Clinical Trials Regulations were finalised in 2004. It was not possible to implement the Clinical Trials Directive and the GCP Directive at the same time because the Clinical Trials Directive required implementation by 1 May 2004 whilst the GCP Directive was not published until 9 April 2005.

The following amendments to the Clinical Trials Regulations, which are not part of the GCP Directive implementation exercise, are also proposed:

- (a) the introduction of a new requirement that sponsors notify the licensing authority (the competent authority for the purposes of the Clinical Trials and GCP Directives) of serious breaches of good clinical practice or the trial protocol where he becomes aware of them. This is implemented by regulation 16 of these Regulations). The purpose of the amendment is to enhance patient safety by seeking to ensure that the licensing authority is aware of crucial breaches and can take appropriate enforcement action.
- (b) extending the power of the enforcement authority to issue “infringement notices” (warning notices) under regulation 48 of the Clinical Trials Regulations to cover breaches of regulation 12 of the Clinical Trial Regulations, namely a failure to hold a trial authorisation and/or obtain ethical approval. This is implemented by regulation 25(a). This will facilitate the enforcement authority obtaining compliance with Regulations.
- (c) modifying the requirement at regulations 17, 24, 38 & 44 that fees payable on an application to the licensing authority under the Clinical Trials Regulations must accompany the application to enable electronic payment and bulk payment to take place. This is implemented by regulations 11, 13, 19 and 23(b). The purpose of this is to facilitate the application process for applicants.

7.3 A 12 week consultation exercise on the implementation of the GCP Directive and the 3 additional proposed changes closed on 7 February 2006. The consultation document was distributed to over 2000 stakeholders, including the NHS, industry trade associations, hospital trusts and patient associations. 75 consultation responses were received. Of the 75 responses received, 41 made no comment and 34 provided specific comments of which 3 stated that they had no concerns and 8 voiced concerns about three specific issues. The three specific concerns raised were:

- the impact of the GCP Directive on those currently unauthorised trials (2);
- additional cost and bureaucracy (4); and
- changes to the wording of the principles of GCP (2).

An analysis of the consultation responses is contained in the regulatory impact assessment (RIA) which accompanies this document.

- 7.4 In the main, the respondents identified the need for further information / clarification on the following issues:
- (a) the time period for which ethics committees would be required to retain documents (13 responses)¹;
 - (b) the format and content of the investigator's brochure (6);
 - (c) the content of the trial master file (4); and
 - (d) the definition of serious breach of GCP that has to be reported to the licensing authority (11);
- 7.5 In response to request (a) and (d), the MHRA has ensured that these Regulations have been drafted to clarify the position (see regulations 28 and 16). In response to request b) and c) the MHRA has agreed to provide further guidance.
- 7.6 Information about the new requirements will be published on the MHRA website (www.mhra.gov.uk). In addition, guidance on the issues that were raised in the consultation exercise will be published on the website when the Regulations are laid before Parliament. The specific areas for which further guidance will be provided are outlined in the RIA which accompanies this document.

8. **Impact**

A RIA is attached to this memorandum.

9. **Contact**

Dr Brian Davis
Medicines and Healthcare products Regulatory Agency
Email address: brian.davis@mhra.gsi.gov.uk

¹ The number in brackets indicates the number of respondents who have raised that issue

REGULATORY IMPACT ASSESSMENT

1. TITLE OF PROPOSAL

Implementation of Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice (GCP) as regards investigational medicinal products for human use, as well as the requirements for authorisation of manufacturing or importation of such products (**The GCP Directive**) and other miscellaneous amendments.

2. PURPOSE AND INTENDED EFFECT OF MEASURE

(i) The objective

To amend the UK Clinical Trials Regulations² (**The principal Regulations**) to implement the GCP Directive; the Regulations implement the Clinical Trials Directive³. Since the Regulations anticipated some of the provisions of the GCP Directive, the objective is to bring their wording in line with the GCP Directive, add required new regulations (the measure) as well as to introduce additional minor changes that will enhance patient safety or facilitate compliance with the Regulations.

The amending Regulations 2(d), 3(b), 4, 5, 9(a), 14, 18, 20 to 22, 23(a), 25(c), 26(d), 27(3), 28(b) and 31 implement the GCP Directive. In particular they make provision for the following matters:

- (a) delegation of functions by the sponsor (regulation 3(b));
- (b) imposition of new requirements on sponsors/investigators in relation to the investigator's brochure and trial documentation (regulation 4, 18, 25(c) and 26(d));
- (c) functions of the Member State and the competent authority under the GCP Directive to be exercised by the licensing authority, unless the functions fall to be performed by the exercise of powers and duties conferred on another person or body under or by virtue of the principal Regulations (regulation 2(d) and 5). This is to ensure that inspectors meet the standards, and comply with the procedures, set out in the Directive;
- (d) changes to the obligations of ethics committees (regulation 9(a) and 28(b));
- (e) the sharing of information between ethics committees and the licensing authority (regulation 14);
- (f) amendment of the provisions on the scope of, and procedures for, manufacturing authorisations and the obligations of the holders of such authorisations (regulations 20 to 22, 23(a) and 31); and

² The Medicines for Human Use (Clinical Trials) Regulations 2004 SI [2004/1031] which implement Directive 2001/20/EC, the Clinical Trials Directive.

³ DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

(g) a revision of the conditions and principles of good clinical practice which apply to all trials (regulation 27(3)).

Amending Regulations 11, 13, 19 and 23(b) remove the requirement that the appropriate fee must accompany applications for clinical trial authorisations, applications to amend clinical trial authorisations, applications for manufacturing authorisations and applications to amend manufacturing authorisations, where the applicant has made arrangements with the licensing authority for the payment of the fee at a different time.

Amending Regulation 16 makes provision for a new requirement that serious breaches of good clinical practice or the trial protocol must be notified to the licensing authority.

Amending Regulation 25 extends the application of the infringement notices regime in the principal Regulations to a) breaches of the sponsor's responsibilities for the investigator's brochure; b) the requirement not to start or conduct a clinical trial without a clinical trial authorisation or a favourable opinion from an ethics committee; c) the requirement of the sponsor to report serious breaches of good clinical practice or the trial protocol; and d) the requirements relating to the trial master file and archiving.

Amending Regulation 26 makes the following a criminal offence: a) breach of the sponsor's responsibility for the investigator's brochure; b) breach of the requirement on a sponsor to report serious breaches of good clinical practice or the trial protocol; and c) breach of the trial master file and archiving requirements.

Amending Regulations 2(a) to (c), 3(a), 6 to 8, 9(b), 10, 12, 15, 17, 24, 27(2) and (4), 28(a) and (c), 29, 30, 32 and 33 correct various errors in the principal Regulations.

Most of these changes would not increase the regulatory burden because the changes brought about by the GCP Directive reflect current good clinical practice in the UK. Some of the provisions bring principles and details of ICH GCP guidelines into legislation nevertheless they are accepted current practice both for industry and academic researchers.

There may be sponsors that do not follow good clinical practice guidelines. They could experience an increased regulatory burden from certain amendments to the Regulations. As a sponsor they would be required to

- Ensure that clinical trials are conducted in accordance the conditions and principles of GCP. These would not materially change the current standards;
- Prepare the investigators brochure (IB) in a format that enables a clinician or potential investigator to understand it and make an unbiased risk-benefit assessment of the appropriateness of the proposed clinical trial;
- Validate and update the IB at least once a year;
- Maintain a trial master file in accordance with the specificities of each phase of the clinical trial which enables both the conduct of a clinical trial and the quality of the data produced to be evaluated and shows whether the investigator and the sponsor have complied with the principles and guidelines of good clinical practice and with the applicable requirements;
- In conjunction with the investigator, retain the essential documents for at least five years after completion of the clinical trial;

- Archive the essential documents in a way that ensures that they are readily available upon request to the competent authorities;
- See to it that the medical files of trial subjects are retained for at least five years after the conclusion of the trial;
- Document any transfer of ownership of the data or documents and ensure that the new owner assumes responsibility for data retention and archiving;
- Ensure that individuals within his organisation are appointed who are responsible for archives;
- Restrict access to archives to the named individuals responsible for archives;
- Store essential documents on media such that they remain complete and legible throughout the required period of retention and can be made readily available to the competent authorities on request;
- Ensure that any alteration to records is traceable;

Chapter 3 of the GCP Directive is concerned with the requirements in respect of authorisation of manufacture of investigational medicinal products. Proposed amendments to the Clinical Trial Regulations necessary to implement the further provisions relating to manufacturing will not significantly alter the current procedures and are not expected to create an additional regulatory burden.

Additional proposed amendments to the principal Regulations

In addition to the requirements of the GCP Directive the licensing authority has proposed the following amendments to enhance patient safety and facilitate compliance with the Regulations and invited comments on them as part of the consultation to amend the Principal Regulations:

- (a) To require that the licensing authority should be notified if a sponsor becomes aware of serious breaches of Good Clinical Practice or the protocol. A "serious breach" in the regulations is defined as a breach which is likely to effect to a significant degree:
 - (i) the safety or physical or mental integrity of the subjects of the trial; or
 - (ii) the scientific value of the trial
- (b) To provide the power to issue an infringement notice in relation to a breach of the requirement (Regulation 12) to hold a Clinical Trials Authorisation (CTA) or obtain ethical approval;
- (c) To allow a sponsor to make a valid application to the competent authority without the applicable fee on condition that arrangements are in place to pay the applicable fee.

(ii) Background

- (a) The European Commission on the 4 April 2001 adopted Directive 2001/20/EC. The Directive covers the implementation of good clinical practice in conduct of clinical trials for human use in the European Union.
- (b) Article 1(3) of Directive 2001/20/EC provides that the Commission will publish the principles of good clinical practice and detailed guidelines in line with those principles.

- (c) The Medicines for Human Use (Clinical trials) Regulations 2004 [SI 2004/1031] which came into force on the 1 May 2004 implements Directive 2001/20/EC into UK legislation.
- (d) The Commission publicly consulted on the draft text on 1 July 2004 for comment by 31 July 2004. UK Ministers wrote to key stakeholders to draw their attention to the Commission's consultation.
- (e) The text of the draft GCP Directive was agreed at Standing Committee on 27 September 2004.
- (f) Commission Directive 2005/28/EC laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products was adopted on the 8 April 2005.
- (g) The Directive entered into force on the twentieth day following that of its publication in the *Official Journal of the European Union*, on the 9 April 2006. The UK must bring into force the laws, regulations and administrative provisions necessary to comply.
- (h) The Government consulted on the GCP Directive on 15 November 2005 for comment by 7 February 2006.

Current UK arrangements

The principal Regulations are the present UK arrangements for regulating the commencement and conduct of clinical trials of human medicines. In addition to transposing the Clinical Trials Directive, they also transposed the requirements of a draft version of the Commission's GCP Directive, which the Commission was developing with Member States prior to the Clinical Trial Regulations coming into force. They therefore already include provisions for (a) the principles of GCP, (b) rules of procedure for ethics committees, (c) the sponsor's responsibilities, (d) minimum requirements for manufacturing and import authorisation, and (e) responsibilities for functions under the GCP Directive. We propose to amend these provisions to bring them in line with the adopted text and add provisions on (a) the format and updating of the investigators brochure, (b) the retention of data and archiving for the trial master file and (c) require notification of serious breaches of GCP and right to issue an infringement notice where serious breaches of GCP are not notified to the competent authority.

(iii) Risk Assessment

Risk to clinical trial subjects

One of the primary aims of the GCP Directive is to place the principles and detailed guidelines for good clinical practice on a statutory basis in order to protect subjects who volunteer for clinical trials.

Although the risks are weighed against the potential benefits before a trial is allowed to commence risks may still be present. The purpose of setting GCP standards and providing detailed GCP guidance for sponsors and investigators is to minimise that risk.

The participation of subjects in trials, when the people responsible do not conform to an accepted standard of GCP (the hazard) could lead to the subjects experiencing considerable personal risk and inconvenience (the harm).

Whilst the MHRA is not aware of extensive statistics on the potential for risk it has inspected over 100 trials through its voluntary GCP inspection programme. Inspectors have identified some critical instances of non-compliance with GCP. They also found evidence of inadequate handling of IMPs, violation of the inclusion/exclusion criteria whereby investigators allowed patients to participate in trials who should have been excluded for medical reasons and inadequate reporting of serious adverse events. Studies have also been stopped because of risks to patients; in one case, a serious error in the dose of medicine administered resulted from a miscalculation when the trial supplies were ordered. In 2002-03 the MHRA received about 16,000 reports of serious unexpected adverse reactions to some 1200 IMPs in some 2000 clinical trials. While most of these would be idiosyncratic responses to the IMP, other causes, such as non-compliance with GCP and good manufacturing practice (GMP) cannot be ruled out.

Medication errors occur frequently in normal medical practice and are equally likely to occur in clinical trials. In a survey by the Commonwealth Fund in 2002 18% of UK respondents said they had experienced a medication error or other medical error in the past 2 years⁴. There were 85,342 incident reports to the National Reporting and Learning System (NRLS) between November 2003 and 31 March 2005 affecting 86,142 patients. The majority of incidents (68%) resulted in no harm to patients but about 1% led to severe harm or death⁵.

Risk to public health

Public Health is put at risk when the results of clinical trials are not collected, recorded and analysed in accordance with the principles of GCP. As a result, they cannot be audited and verified before being used to impact on public health e.g. through a publication that changes medical prescribing practice or as evidence to support applications to place a medicine on the market.

The submission of data to support a Marketing Authorisation (MA) or a publication that will change prescribing habits from clinical trials, which have not been carried out to accepted standards (the hazard), could lead to a risk to public health if the licensing authority (LA) or a journal accepted the data and mistakenly authorised a medicine for marketing or published the results (the harm)

Serious clinical research misconduct and fraud also undermine the accuracy of data used to impact on public health as illustrated in Appendix A. Organisations that oversee the standards for conducting clinical trials such as The Royal College of Physicians, the Academy of Medical Sciences, Universities UK, the Committee on Publication Ethics (COPE), and the General Medical Council (GMC) have voiced concerns about the detection and handling of research misconduct in the UK for several years.

⁴ Healthcare Commission Report 2005. P33 (accessed 19.09.05).

⁵ NPSA website [<http://www.npsa.nhs.uk/web/display?contentId=4229>] accessed 19.09.05

In response to growing concern, influential clinicians and clinical journal editors met in Edinburgh in 1999 and agreed that something decisive had to be done about research misconduct.⁶ COPE has heard over 200 cases of alleged misconduct since it was established in 1997⁷.

However, the report of the COPE annual conference in October 2003 published on their website (<http://www.publicationethics.com>) shows that those bodies responsible for voluntary oversight of research are reluctant to take on this responsibility.

The participants welcomed the Department of Health's Research Governance Framework which includes guidance on good clinical practice and claimed that incidences of research misconduct had fallen since its introduction. They also felt that MHRA statutory GCP inspections of trials of medicines, introduced by the UK regulations, will help to maintain the standards of clinical research.

The pharmaceutical industry has also recognised the problem and use sophisticated statistical methods to check data for possible fraud^{8,9}. The legislation will also discourage fraud by introducing criminal penalties for falsifying data. The arrangements, including inspections against mandatory standards, should make such fraud less likely to go undetected.

A UK Panel for Research Integrity in Health and Biomedical Sciences announced in April 2006¹⁰ will provide the focus for promotion of good practice in research in health and biomedical sciences. Established initially for 3 years, the Panel will aim to embed a culture of good conduct into the research system. The intention is to reinforce a zero-tolerance approach to misconduct in all its forms. The Panel's work will be independent of government, funders, industry and universities. The Panel will not take on any responsibility for dealing with allegations of research misconduct. It will remain the responsibility of the employer and or research sponsor to take appropriate action.

Whilst the limited evidence available suggests that the majority of clinical trials conducted in the UK already broadly conform to agreed standards and principles of GCP, the introduction of regulations will make compliance mandatory and provide appropriate enforcement powers, which together are expected to further reduce the risks to patients without inhibiting high quality clinical trials. The systems of inspection and audit required against the mandatory standards set by the new legislation will provide a stronger assurance of the credibility of data and reduce the risk that inaccurate or fraudulent data will be used to support the marketing of a medicine or a change to prescribing practice.

⁶ Lancet. Commentary – Farthing, Horton, Smith. Vol – 356, Number 9247, 16 Dec 2000.

⁷ BMJ Editorial: - F. Godlee. Dealing with editorial misconduct. BMJ 2004;329:1301-2,

⁸ Buyse M, George SL, Evans S, Geller NL, Ranstram J, Scherrer B et al. The role of biostatistics in the prevention, detection and treatment of fraud in clinical trials. Stat Med 1999; 18:3435-51.

⁹ Taylor RN, McEntegart DJ, Stillman EC. Statistical techniques to detect fraud and other data irregularities in clinical questionnaire data. Drug Inform J 2002;36: 115-25.

¹⁰ <http://www.universitiesuk.ac.uk/mediareleases/riolaunch.asp>

3. OPTIONS

Option 1: Continue to rely on existing arrangements. The Principal Regulations are the present UK arrangements for regulating the commencement and conduct of clinical trials of human medicines. In addition to transposing the Clinical Trials Directive, they also transposed the requirements of a draft version of the Commission's GCP Directive, which the Commission was developing with Member States prior to the Clinical Trial Regulations coming into force.

They therefore already include provisions for (a) the principles of GCP, (b) rules of procedure for ethics committees, (c) the sponsor's responsibilities, (d) minimum requirements for manufacturing and import authorisation, and (e) responsibilities for functions under the Directive.

The provisions in the adopted text of the GCP Directive differ materially from the provisions of the draft text and associated assumptions used as a basis for the Principal Regulations. Under this option, the UK would fail to comply with its obligation under European Community law to implement the GCP Directive into national law.

Option 2: Implement the GCP Directive by amending the principal Regulations and make other miscellaneous amendments.

Some provisions of the principal Regulations anticipated the requirements of the GCP Directive but were based on a draft version of the Directive. The provisions of the finally published GCP Directive differ materially from that draft text. This option would amend the principal Regulations to align them with the provisions of the adopted text of the GCP Directive. In addition this option would amend the principal regulations to (a) introduce additional minor changes that will enhance patient safety or facilitate compliance with the Regulations and (b) correct various errors in the principal Regulations (see section 2 (I) for details of the amending regulations).

4. BENEFITS

Option 1: Continue to rely on existing arrangements

- Would avoid the effort of introducing change. Feedback during the Commission consultation on the GCP Directive during July 04 indicated that academia and industry had few concerns about the proposed requirements because they were already complying with most of them although industry would prefer to keep the current text of the ICH principles of GCP rather than change to the wording of the GCP Directive;
- Would avoid any additional costs of implementing change for industry and academia, as set out in Section 5 below;
- Would avoid any additional resources needed by the MHRA

Option 2: Implement the Directive by amending the Regulations

The proposed amendments to the principal Regulations would benefit trial participants by further ensuring that their rights, safety and well-being are

protected by providing a statutory basis for a number of aspects of the conduct of clinical trials that introduce risks for them. They will require that all clinical trials be conducted according to additional detailed aspects of GCP, which will strengthen the existing situation that relies on GCP guidance.

The amending regulations will:

- (a) Allow sponsors to delegate their functions when necessary (regulations 3(b)
- (b) Ensure that clinicians and potential investigators can make an unbiased risk-benefit assessment of the appropriateness of the proposed clinical trial from the investigator's brochure and that it is updated at least once a year (regulation 4);
- (c) Ensure that the sponsor keeps essential documents that enable both the conduct of the trial and the quality of the data produced to be evaluated; holds them readily available to the licensing authority for inspection; and makes suitable arrangements to retain them for at least 5 years after the conclusion of the trial (regulation 18, 25(c) and 26(d));
- (d) Ensure that inspectors meet the standards and comply with the procedures set out in the GCP Directive (regulations 2(d) and 5);
- (e) Ensure that ethics committees retain documents pertaining to their opinions for a minimum period (regulation 28(b));
- (f) Improve the communication between ethics committees and the licensing authority (regulation 14);
- (g) Ensure that manufacturers have appropriate staff, premises, equipment and facilities and comply with good manufacturing practice standards (regulations 20 to 22, 23(a) and 31);
- (h) Provide wording for the conditions and principles of good clinical practice that is consistent with the Clinical Trials Directive and GCP Directive (regulation 27(3));
- (i) Improve the procedure for making applications to the MHRA related to clinical trials by allowing applicants to make arrangements with the licensing authority for payment of the fee other than at the time of application (regulations 11, 13, 19, and 23(b));
- (j) Protect trial participants by requiring sponsors to notify the licensing authority of serious breaches of good clinical practice or the trial protocol (regulation 16);
- (k) Reduce non-compliance with the principal Regulations by allowing the licensing authority to serve infringement notices for non-compliance relating to (a) the sponsor's responsibilities for the investigator's brochure, (b) the requirement not to start or conduct a clinical trial without a clinical trial authorisation or a favourable opinion from an ethics committee, (c) the sponsor's responsibility to report serious breaches of good clinical practice or the trial protocol, and (d) the requirements relating to the trial master file and archiving A "serious breach" is a breach which is likely to effect to a significant degree- (a) the safety or physical or mental integrity of the subjects of the trial; or (b) the scientific value of the trial. (regulation 25);
- (l) Correct various errors in the principal Regulations (regulations 2(a) to (c), 3(a), 6 to 8, 9(b), 10, 12, 15, 17, 24, 27(2) and (4), 28(a) and (c), 29, 30, 32, and 33).

The proposed amendments to the UK Clinical Trial Regulations would benefit public health by providing a statutory basis for a number of detailed aspects of the conduct of clinical trials that pose a threat to public health. They will

provide a statutory basis for some additional detailed aspects of GCP standards, supported by powers of inspection and enforcement, which will help to ensure that all trials are conducted according to those international standards and therefore help minimise the considerable personal risk and inconvenience to participants in trials that do not conform to those standards.

They would introduce:

- Additional details of the standards for manufacture and import of investigational medicinal products, supported by powers of inspection and enforcement which will help to ensure that trial participants are not exposed to poor quality medicines;
- A requirement that sponsors make arrangements to accurately collect, record, analyse and report clinical trial findings as set out in the protocol and archive the data for future reference. Sponsors, investigators, statisticians and auditors can then audit and verify the data before it is published or used to support an application to place a medicine on the market. Medical practitioners from the UK or other countries frequently rely on results published in influential journals to change their medical prescribing practice. This will avoid the public health risks of exposing large numbers of patients to the risk of being prescribed a medicine whose benefit has been overestimated or whose risk of harm has been underestimated
- A statutory basis for appropriate qualifications and training for MHRA inspectors. This would help deter unethical and unscientific practices of research misconduct including fraud by ensuring high quality inspections of the conduct of clinical trials supported by powers of enforcement. This would reduce the unacceptable risk to patients who might participate in studies that will not provide useful information about the IMP under test. [See section on research misconduct above];
- Changes to the environment for conducting clinical trials that would make the UK attractive to *bone fide* researchers because they wish commence and conduct clinical trials that conform to accepted standards of GCP. This would allow patients with diseases that are not adequately treated the opportunity to benefit from new potential treatments;

The proposed amendments to the principal Regulations would benefit economic aspects of conducting clinical trials to develop new medicines or identify new uses for existing medicines. They will

- Fully implement the provisions of the GCP Directive, thereby ensuring that the UK complies with its obligations under European Community law;
- Ensure that clinical trials are subject to a legal obligation to comply with additional details of GCP standards and that the licensing authority has a statutory duty to appoint appropriately qualified and trained inspectors and see to it that they follow required inspection procedures. The economic value cannot be quantified directly, however, a company could lose the costs of developing a medicinal product, of the order of £500 million¹¹, if the standards and data are not in compliance and therefore fail to support an application for a marketing authorisation.
- Allow companies from United States, Japan and other countries to conduct clinical trials in the UK when they require international GCP

¹¹ Source ABPI

standards to support applications for marketing authorisation in their own country.

The principal Regulations already require sponsors to notify the licensing authority of certain matters that may indicate non-compliance. Sponsors of a clinical trial must notify the licensing authority of all site closures either under Regulation 30 (Urgent safety measures) or Regulation 29 (Conduct of a clinical trial in accordance with clinical trial authorisation etc) of the principal Regulations. To extend these provisions amending regulation 25 would require a sponsor to notify the licensing authority if he becomes aware of serious breaches of GCP or the protocol.

Regulation 47 and Schedule 9 of the principal Regulations provide the licensing authority already has with powers to inspect trials which they think contravene the requirement to hold a current valid Clinical Trial Application under Regulation 12 of the principal Regulations. However it does not have certain related enforcement powers. Amending regulation 25 will provide the licensing authority with the power to issue an infringement notice in relation to such a breach.

Business sectors affected

All parts of the innovative pharmaceutical industry will be affected. There will be a lesser impact on the generic sector. The NHS, universities, charities and others who undertake non-commercial clinical trials will also have to comply with the amendments to the Regulations. The following list shows the approximate numbers of organisations in each sector:

- companies conducting trials in the UK (total) 400
- UK based pharmaceutical companies 130
- UK hospitals conducting non-commercial trials 200

Companies can be classified as large or small according to their per cent market share as follows:

- companies in ABPI members list 100
- market share > 0.5% 25; market share > 5% 3

Issues of Equity or Fairness

The proposed Option 2 will provide participants in clinical trials with reassurance that there are additional controls on the conduct of the trial, the safety and quality of the medicinal product and that the data will be credible and verifiable. It will ensure fairness to consumers by providing reassurance that the data used to decide whether a medicine is marketed or prescribed for a certain condition conforms to accepted standards. In addition, ensuring high standards for the conduct of clinical trials in the UK will avoid costly errors in the data from clinical trials and encourage the pharmaceutical industry to invest in development of new medicines in the UK. Harmonisation of clinical trials legislation within the Community will ensure fairness for companies by ensuring that the standards and procedures applied in the UK are the same as in the rest of the European Community.

Furthermore, provisions in the GCP Directive allow Member States to introduce “specific modalities” – that is working practices, for researchers

involved in non-commercial research without the participation of the pharmaceutical industry. This will allow Member States to make allowance for the conditions under which non-commercial research is conducted by public researchers particularly as they relate to manufacturing and import requirements and the documentation to be submitted and archived for the trial master file are concerned. These specific modalities will be the subject of Commission guidance to ensure that Member States do not introduce different working practices so that differences in regulation would inhibit the commencement and conduct of multinational trials in the Community. Consideration will be given to further amending the Regulations when the Commission guidance is available.

5. COSTS

(i) Anticipated Costs under option 1

Option 1: Continue to rely on existing arrangements

This option would not change the current costs for pharmaceutical companies, medical research charities, universities or NHS Trusts, but would not implement some aspects of the GCP Directive including: (a) the specified wording for the principles of GCP, (b) the appropriate scope and procedures manufacturing authorisations, (c) the format and retention period for the investigator's brochure, (d) retention of documents and communication with the competent authority by ethics committees, and (e) responsibilities of MHRA in relation to qualifications of inspectors and inspection procedures. It would not change the costs to Government unless the European Court of Justice applied penalties to the UK for not fully implementing the Directive.

(ii) Anticipated costs under option 2

Option 2: Implement the Directive by amending the Regulations

Activities for which fees are proposed

MHRA sets fee levels that reflect the time and resources required to complete their activities. It does not expect to increase its fees as a result of the proposed amendments to the Regulations. There are no charges for applications to NHS research ethics committees or GTAC.

Costs of commencing and conducting a clinical trial to conform with the amended principles of GCP (Articles 2-5; Amending Regulation 27(3))¹²

The proposed amendment 27(3) would replace Schedule 1 Part 2 (conditions and principles that apply to all clinical trials - which were based on the principles from ICH GCP), with principles based on Articles 2 to 5 of the GCP Directive and conditions based on Article 3 of the GCP Directive. The amended principles are essentially identical to the current Regulations but with some change to the wording. The current Regulations require sponsors to conduct clinical trials in accordance with the conditions and principles of ICH GCP. The MHRA could not exclude the possibility that there could be sponsors who do not comply with the conditions and principles of GCP. The consultation document (MLX 328), therefore, specifically sought views on whether this proposed amendment would result in increased costs. One

¹² Articles refer to the relevant article in the GCP Directive, Amendments refer to the associated regulation in the proposed Medicines for Human Use (Clinical Trials) Amendments.

respondent conjectured that this might increase costs for certain academic trials.

Costs of implementing requirements for ethics committees (Article 6; Amending Regulation 9(b), 14 and 28(b))

The proposed Regulation 9(b) would amend Regulation 15 to allow an ethics committee to consider the summary of product characteristics relating to an investigational medicinal product used in accordance with its marketing authorisation instead of an investigator brochure. The proposed Regulation 28(b) would amend Schedule 2 (additional provisions relating to ethics committees) to require an ethics committee to retain all the documents relating to a clinical trial on which it gives an opinion for at least three years after (a) the conclusion of a trial that proceeds or (b) the date of the opinion for a trial that does not proceed. The proposed Regulation 14 would insert a new Regulation 27A allowing the licensing authority and an ethics committee to disclose to each other information acquired in carrying out their respective functions under the Regulations to assist the other body to carry out its functions. We do not expect that the requirement for ethics committees to retain documents and the communication between the competent authority and an ethics committee would result in additional costs because this is already current practice.

Costs of implementing requirements for sponsors (Article 7; Amending Regulation 3(b))

The proposed Regulation 3(b) would amend Regulation 3, which provides detailed provisions on the responsibilities of sponsors, to clarify that the sponsor may delegate any or all of his trial related functions but remains responsible for them. We do not expect this would result in additional costs.

Costs of implementing the requirements for the investigator's brochure (Article 8; Amending Regulation 4)

The current Regulations do not make provisions for the format and updating of the investigator's brochure but they are part of ICH GCP guidance. The proposed Regulation 4 would introduce a new Regulation 3A to require the sponsor to present the investigator's brochure in a specified format and validate and update it at least once a year. This is part of ICH GCP guidance on the format and content of the investigator's brochure. As this is current practice, we do not expect this would result in additional costs.

Costs of implementing the requirements for manufacturing and import authorisation (Articles 9-15; Amending Regulation 20 to 22, 23(a) and 31)

The current Regulation 40, Schedules 7 and 8 provide most of the requirements set out in these Articles. They require authorisation for total and partial manufacture of IMPs including for products for export and imports from third countries. They also require all the minimum requirements for making an application for a manufacturing authorisation in Article 10 and the requirements for verifying the particulars and responding to an application within 90 days or to a request for change within 30 days and the provision to stop the clock while waiting for additional information from the applicant.

The current Regulation 41 and Schedule 7 also place requirements on the holder of a manufacturing authorisation to notify the licensing authority of any changes he wishes to make to any of the particulars supplied, in particular

relating to the Qualified Person, to allow agents of the licensing authority access to his premises at any time, to place the necessary facilities at the disposal of the QP to comply with the principles and guidelines for GMP. They also provide powers to the licensing authority to suspend or revoke a manufacturing authorisation as a whole or in part, if the holder fails to comply with the relevant requirements.

The proposed Regulation 20 would amend Regulation 40 so that, before the licensing authority will grant a manufacturing authorisation, the applicant must have at his disposal the services of staff in addition to suitable premises, technical equipment and control facilities.

The proposed Regulation 21 would amend Regulation 41 to add that the manufacturing authorisation can apply to the manufacturing process for applications that relate to inactivation of viral or non-conventional agents.

The proposed Regulation 22 would amend Regulation 42 to add that the holder of a manufacturing authorisation must (a) allow the licensing authority access to his premises at any reasonable time and (b) put and keep in place arrangements which enable the Qualified Person (QP) to carry out his duties and provide him the necessary facilities.

Proposed Regulation 23(a) would amend Regulation 44 to allow for the licensing authority to vary the manufacturing authorisation to change the manufacturing process and staff, including the QP.

Proposed Regulation 31 would amend Schedule 6, paragraph 2 to include in the particulars that accompany an application for a manufacturing authorisation, a statement describing the pharmaceutical forms of the investigational medicinal products

These additional provisions are already standard practice. We therefore do not expect any additional costs will result from the implementation of these provisions of the GCP Directive.

Costs of implementing the requirements for the trial master file and archiving (Articles 16-20; Amending Regulations 18, 25(c) and 26(d))

The Regulations do not provide for the format, content and archiving of the essential clinical trial documents that make up the trial master file. However ICH GCP guidelines provide guidance on those aspects of the trial master file.

The proposed Regulation 18 would introduce a new Regulation 31A (Trial master file and archiving) which would oblige the sponsor to keep a trial master file for a clinical trial that contains essential documents relating to the clinical trial and specifies (a) the nature and scope of those documents, (b) their availability for inspection by the licensing authority and auditors and (c) how long the sponsor and investigator must keep the essential documents and medical records.

It also obliges the sponsor to (a) make arrangements for archiving the essential documents (b) to restrict access to the documents and (c) to document transfer of the documents and responsibilities to a new owner.

Industry sponsors must comply with the ICH GCP guidelines as the standard required to support a marketing authorisation application. This will also be the case for most non-commercial researchers who comply with the ICH GCP principles and conditions.

Proposed Regulation 25(c) would amend regulation 48 to allow the licensing authority to serve an infringement notice for a contravention of Regulation 31A.

We were not able to estimate how many sponsors if any would incur additional costs as a result of implementing these provisions of the GCP Directive. The consultation document (MLX328), therefore specifically sought views on whether this proposed amendment would result in increased costs. The comments of 4 respondents indicated concern about unnecessary bureaucracy and additional costs: one proposed that an investigator brochure should not be necessary for a single investigator trial; one was not convinced that the proposed changes will not add substantial cost and bureaucracy to small academically led trials; one was concerned about increased costs to small businesses; and one said the implementation costs do not appear to be clearly thought through and will need fleshing out and it is felt that the regulation will add further to the large burden of paperwork involved in conducting clinical trials, for instance lack of differentiation between large high risk trials and small low risk trials.

Costs of implementing requirements for the qualifications and training of inspectors (Article 21; Amending Regulations 2(d) and 5)

The MHRA currently has minimum criteria for the educational background and experience of people being considered as inspectors and a programme for training newly appointed and experienced inspectors in the procedures for clinical research, and relevant Community and national legislation and guidelines. It maintains records of their training and experience and provides them with written documentation of standard operating procedures, duties, responsibilities and ongoing training requirements as well as a suitable means of identification. It also requires a signed statement of interests from each inspector. MHRA also has a procedure for establishing a team of inspectors.

The proposed amendments would place these MHRA responsibilities on a statutory basis. The proposed Regulations 2(d) and 5 would amend Regulations 2 and 4 respectively to make the licensing authority (the competent authority of the United Kingdom acting through the MHRA) responsible for functions under the GCP Directive. We do not expect that MHRA will incur additional cost as a result of implementing these provisions.

Costs of implementing requirements for inspection procedures (Articles 23-30; Amending Regulations 2(d) and 5)

The current MHRA inspection procedures are in line with the requirements of the GCP Directive but some of them are not on a statutory basis. Inspections may take place before, during or after a clinical trial, as part of verification of applications for a marketing authorisation and as follow up to the granting of authorisation. They may be requested or co-ordinated by the European Medicines Agency where appropriate and are conducted in accordance with

Community inspection guidance documents agreed processes and procedures.

The licensing authority acting through MHRA makes documents available relating to the adoption of good clinical practice and has a legal and administrative framework within which their good clinical practice inspections operate, with definition of powers of inspectors for entry into clinical trial sites and access to data. On request inspectors from other Member States may have access to clinical trial sites and data.

MHRA is responsible for appointing an adequate number of inspectors to verify compliance with good clinical practice and for maintaining procedures for examining management, planning, performance, monitoring and recording of clinical trials. It has a procedure for appointing experts to accompany inspectors as needed, requesting inspections/assistance from other Member States, co-operating in inspections in another Member State, and arranging inspections in third countries. It maintains records of national and international inspections and their follow up with a statement of compliance status.

Legislation and rules are in place in the UK that ensure that confidentiality is respected by inspectors and other experts including the provisions of Directive 95/46/EC with regard to personal data. MHRA restricts access to inspection reports, only making them available to the inspected organisation/individual, other Member States Competent Authorities, the Commission and the European Medicines Agency and in an appropriate format in accordance with UK legislation.

The proposed amendments would place these MHRA responsibilities on a statutory basis. The proposed Regulations 2(d) and 5 would amend Regulations 2 and 4 respectively to make the licensing authority (the competent authority of the United Kingdom acting through the MHRA) responsible for functions under the GCP Directive. We do not expect that MHRA will incur additional cost as a result of implementing these provisions.

Costs of implementing additional amendments to the Principal Regulations.

- (a) ***The additional requirement to notify the licensing authority of serious GCP non-compliance (Amending Regulations 16 and 26):*** The proposed Regulation 16 would introduce a new regulation 29A that requires the sponsor to notify the licensing authority in writing of any serious breach of GCP or the clinical trial protocol. Proposed Regulation 26 would amend Regulation 49 to make it a criminal offence to contravene the new regulation 29A. This is not expected to be an additional burden or create an additional expense.
- (b) ***The additional powers to issue an infringement notice in relation to Regulation 29A (Amending Regulation 25):*** Proposed Regulation 25 would amend Regulation 48 to provide the licensing authority with additional powers to issue an infringement notice where failure of a sponsor to provide notifications under Regulation 29A has been established. This is not expected to create an

additional burden and will be administered as part of established inspection costs.

(c) ***Making a valid application to the competent authority without the applicable fee (Amending Regulations 11, 13, 19 and 23(b)):***

The following proposed amendments would permit a sponsor to submit a valid application without it being accompanied by the applicable fee on condition that arrangements are in place to pay the applicable fee. Proposed regulation 11 would amend Regulation 17 in the case of a request for authorisation to conduct a clinical trial; proposed regulation 13 would amend Regulation 24 in the case of a valid notice of amendment; proposed Regulation 19 would amend Regulation 38 in the case of an application for a manufacturing authorisation and proposed Regulation 23(b) would amend Regulation 44 in the case of a variation of a manufacturing authorisation. These amendments are expected to facilitate the process of making applications. They are not expected to create an additional burden and will be administered as part of licensing administrative costs.

6. CONSULTATION WITH SMALL BUSINESS: THE SMALL FIRMS' IMPACT TEST

In the RIA for the implementation of the Clinical Trials Directive, which included many of the provisions of the GCP Directive, we identified 170 companies conducting trials in the UK with 2 products or less. MHRA discussed proposals with one small research-based pharmaceutical company involved in developing one biotechnology product. The company surveyed did not consider that the proposed Clinical Trials Regulations would introduce a regulatory burden that would slow down development of medicines by the company, nor did it feel that the additional costs would inhibit its activities. The company already worked to internationally recognised standards for GCP.

The Association of the British Pharmaceutical Industry (ABPI) provided estimates of the impact of implementing the UK Clinical Trials Regulations on small companies (see Appendix B). The companies already worked to GCP and GMP standards. As these standards include the provisions of the GCP Directive we anticipate that they will not incur any major additional costs.

7. COMPETITION ASSESSMENT

Market affected

The proposed Regulations will affect the market that provides the resources and facilities to conduct clinical trials because any increase in the cost of carrying out clinical trials will affect the total cost of bringing medicines to market. They might also affect the upstream pharmaceuticals market indirectly. **The clinical trials market**

Organisations such as research-based pharmaceutical companies, commercial trial centres acting under contract, and a range of non-commercial bodies such as universities, the NHS, and medical research charities undertake most clinical trials. Trials undertaken by or on behalf of pharmaceutical companies comprise the majority of trials and are conducted

on a commercial basis. Although we do not have detailed information about the size and number of players in this market, we do not anticipate that the proposed regulation would have any significant impact on competition because of the low level of costs associated with it relative to the total development costs of a pharmaceutical product. We anticipate that commercial providers of clinical trials will be able to pass on or absorb any additional costs of compliance.

The impact on researchers conducting non-commercial clinical trials will be affected by the “specific modalities” that Member States can introduce for these trials in compliance with the Commission guideline. We cannot estimate the impact on non-commercial researchers until the guideline is available.

8. RESULTS OF CONSULTATIONS

Consultation on the Clinical Trials Regulations

In February 2003, MHRA consulted on proposed Clinical Trials Regulations which anticipated the provisions of the GCP Directive. Over 160 responses were received. Industry was broadly content with the proposed Regulations. However, responses received from those involved in publicly funded trials raised concerns about the possible impact of the regulatory burden on academic research in the UK and suggested that the additional costs of conducting trials would result in fewer trials being funded. The Medical Research Council (MRC) submitted an evaluation of the implications for those involved in publicly funded trials. The major issues of concern raised were (a) arrangements for sponsorship of trials, (b) authorisation process, (c) pharmacovigilance requirements; and (d) inspections for compliance with GCP.

In response to the concerns expressed by the MRC and others involved in publicly funded trials, the MRC and the Department of Health (DH) established a Joint Project to assist trialists and the MHRA by identifying and documenting current best practice in those areas that the Directive seeks to regulate and to provide advice on systems and approaches based on best practice that will comply with the new regulatory regime. The work of the Joint Project was taken forward through six work streams and the project has made considerable progress in identifying acceptable solutions to concerns raised. Where possible, flexibilities were built into the Regulations to accommodate some of the concerns raised by the academic research community, including the issue of sponsorship. The Regulations allow for a collaborative approach to sponsorship of trials; we do not propose to change this in implementing the GCP Directive.

There were also been some representations about the system for ethical review. One of the concerns was that the process should be streamlined to facilitate rapid review. The proposed modification of the ethics committee procedures should help to speed some aspects of ethical review.

Commission consultation on the GCP Directive

The Commission carried out a consultation exercise on a draft proposal for the GCP Directive during July 2004. At the time the Government alerted major stakeholders to the consultation and sought their views on the scope and provisions of the proposed Directive. Whilst they were concerned that the legislation would include principles as well as details of GCP in legislation

they did not raise serious concerns about the provisions. Most of the concerns raised were addressed before the GCP Directive was adopted by changes agreed at Standing Committee.

Ongoing Consultation

Consultation has been ongoing via conferences, workshops and meetings with the key stakeholders – the pharmaceutical industry, ethics committees, those responsible for NHS R & D funding and operations, the MRC and with UK based medical charities UK (e.g. Cancer Research UK). The Government established the UK Clinical Research Collaboration in October 2004, after the implementation of the Clinical Trials Directive, with the goal of making the UK a leader in clinical research. One of its objectives is to work with its partners to streamline the process of regulation and research governance. To achieve this it has been consulting with those affected by the GCP Directive to gather information on any difficulties experienced by sponsors and investigators and any potential solutions.

Consultation on the proposed amendments to implement the GCP Directive

Introduction

The MHRA consulted on the proposed amendments during a 12-week period ending 7 February 2006. It distributed the consultation document (MLX 328) to over 2000 stakeholders and received responses from small and large pharmaceutical companies, contract research organisations, industry associations, laboratory services, ethics committees, NHS hospital trusts, primary care trusts, Royal Colleges, the Medical Research Council and other organisations representing academic researchers, charities supporting publicly funded research, individual investigators and patient associations.

Of the 75 responses, 41 said no comment and 34 provided specific comments of which 3 stated they had no concerns and 8 voiced concerns about three specific issues. The comments and MHRA responses are set out in Annex A.

Further guidance

Most of the comments asked for additional guidance on the following issues:

- Retention time for ethics committees' documents (13)¹³;
- Definition of serious breach of GCP that has to be reported to MHRA (11);
- Specific modalities that will apply to non-commercial trials (11);
- Format and content of the investigator's brochure (6);
- Content of the trial master file (4);
- Format of new requirements for the manufacturing authorisation (2);
- Scope of the exemption for packaging and labelling (1);
- Update of the reference to the Declaration of Helsinki (1);
- Fee levels for marketed products used off label (1);
- Communication between MHRA and ethics committees (1); and
- The consequences of receiving an infringement notice (1).

In response to these requests MHRA has either modified the proposed Regulations or agreed to provide further guidance on the areas that need clarification.

¹³ The number in brackets indicates the number of respondents commenting on that issue.

Specific questions

For the following proposals respondents asked whether:

- A manufacturing authorisation was needed for distribution of IMPs? (1);
- The GCP Directive applied to marketed products in clinical trials? (1);
- The exemption for hospitals and clinics applied to reconstitution of radiopharmaceuticals? (1);
- A sponsor could delegate the duty to report to the MHRA? (2);
- The GCP Directive applies the same standards to generic medicines? (1);and
- There is any exemption from the requirement to have a QP release an IMP? (1).

Policy leads and SOL have agreed responses to these questions and included them in the table of comments and responses for publication.

Concerns

The three specific concerns raised were:

- The impact of the GCP Directive on those currently conducting unauthorised trials (2);
- Additional cost and bureaucracy (4);
- Changes to the wording of the principles of GCP (2).

Policy leads have considered the above concerns:

- Those responsible for research in the NHS have tried to identify any trial of a medicine not yet authorised by MHRA. Few if any should be being conducted without an authorisation: they would be infringing the Clinical Trials Regulations.
- The consultation document specifically sought information on increased costs and bureaucracy that might result from the proposed amendments. No respondents provided specific examples of how the proposed provisions would increase costs or bureaucracy despite the RIA providing a detailed description of the increased requirements for those not currently conducting trials to GCP standards.
- The MRC and a pharmaceutical company were concerned that confusion might arise because the GCP Directive will change the wording of the principles of GCP as they are described in the ICH GCP guideline. MS, industry and academic researchers have made representations to the Commission on this issue but their legal advice is that they must retain the language in the legal texts of the Clinical Trials Directive and the GCP Directive.

9. ENFORCEMENT AND SANCTIONS

The MHRA will be responsible for monitoring and enforcement of the proposed amendments to the Regulations. The powers for this are provided by the Medicines Act 1968 which will be extended to cover the amended provisions. Compliance with GCP and GMP will generally be monitored through the regular inspection programmes. Appropriate enforcement provisions, including both infringement notices and criminal proceedings, will cover offences concerning the amended provisions. Penalties will be commensurate with those specified in Regulation 52 of the principal Regulations.

10. MONITORING AND REVIEW

The impact of the Clinical Trial Regulations is being monitored by groups that have direct access to Government to promote growth and innovation and have a specific interest in the Government's performance in implementing the Clinical Trials Directive. These groups would monitor the impact of the amendments to the Regulations to implement the GCP Directive.

The Pharmaceutical Industry Competitiveness Task Force (PICTF) Clinical Research Group have published performance criteria for implementing the Directive in their Clinical Research Report. The group consists of representatives from the pharmaceutical industry, the Medical Research Council and the Bio industry Association as well as officials from DH RDD, NHS and MHRA. They meet regularly to assess information on Government performance in a number of aspects of conducting clinical trials in the UK including ability of investigators to complete trials, relative costs compared to other countries and quality of data. This Government-industry group will monitor the impact of the amendments to the UK Regulations on the commercial clinical trials environment in the UK.

The Biosciences Leadership Council, which has been formed following the Bioindustries Innovation Growth Team – BIG-T can be expected to take an interest in the impact of the amendments to the Regulations on the development of medicines from the biosciences.

The UK Clinical Research Collaboration established in 2004, brings together most of the key stakeholders that shape the clinical research environment in the UK. One of its objectives is to streamline the regulatory and research governance processes. As part of this it is monitoring the impact of the Clinical Trials Regulations on non-commercial research. It recently published a report "Impact of the EU Directive on Non-Commercial Trials - 6 months on based on a survey to trialists and trial managers (122 responses): its continuing monitoring will be able to assess the impact of the implementation of the GCP Directive.

11. SUMMARY AND RECOMMENDATIONS

The proposed amendments to the Principal Regulations to implement the GCP Directive will impact on the pharmaceutical industry, and those sponsoring publicly-funded clinical trials of medicines in the following ways:

Additional Regulatory Burden

Most of these changes would not increase the regulatory burden because the changes brought about by the GCP Directive reflect current good clinical practice in the UK. Some of the provisions bring details of existing good clinical practice guidelines into legislation nevertheless they are accepted current practice both for industry and academic researchers.

There may be sponsors of publicly-funded research that do not follow some detailed aspects of GCP guidelines. They could experience an increased regulatory burden from some proposed amendments to the Regulations (see Section 2(I) for details).

The additional requirement to notify the licensing authority of a serious non-compliance with GCP is not expected to be an additional regulatory burden. The additional powers for the licensing authority to issue an infringement notice where failure to comply with GCP has been established is not expected to create an additional burden and will be administered as part of established licensing and inspection regime.

The amendment to allow a sponsor to make a valid application to the competent authority without the applicable fee on condition that arrangements are in place to pay the applicable fee should make the procedure for applying for authorisation of a clinical trial easier.

Additional Costs

The evidence available from the responses to the consultation documents and the ongoing consultation suggests that the additional regulatory activities under the proposed amendments to the Regulations will not introduce additional costs for the pharmaceutical industry, MHRA and Ethics Committees as the new requirements are already part of their current practice.

The responses indicated that there might still be a few sponsors of publicly-funded research that do not follow some detailed aspects of good clinical practice guidelines. They could experience increased costs associated with implementing some of proposed amendments to the Regulations.

D. Recommendation

This impact assessment considers two options for implementing the GCP Directive in the UK:

Option 1 – Continue to rely on existing arrangements which would not satisfy the requirements of the Directive and therefore expose the UK to the risk of infraction proceedings

Option 2 – This option would amend the principal Regulations to align them with the provisions of the adopted text of the GCP Directive. In addition this option would amend the principal regulations to (a) introduce additional minor changes that will enhance patient safety or facilitate compliance with the Regulations and (b) correct various errors in the principal Regulations (see section 2 (I) for details of the amending regulations).

This will provide a statutory basis for some detailed aspects of good clinical practice e.g. format, content and updating of the investigator's brochure, and format, content, ownership, retention and access to the essential documents of the trial master file. These requirements will be supported by inspection and enforcement powers that are acknowledged as an important means to maintain the high standard of clinical research in the UK.

After careful consideration I recommend that the Government adopts the option to amend the Principal Regulations to implement the GCP Directive (2005/28/EC)

I have read this document and am satisfied that the benefits justify the costs.

Signature (Minister responsible) *Andrew Burnham*

Date 13th July 2006

Contact point:

Dr Brian Davis
Clinical Trials Unit
MHRA
Tel: 01768 779 640 or 0207 084 0456

RESEARCH MISCONDUCT AND FRAUD

Recent research misconduct

This issue received public attention in 2005 as a result of the withdrawal of papers on the creation of human embryonic stem cells^{14 15} which were heralded as a scientific breakthrough when first published. Also last year the Office of Research Integrity reported a multi-million dollar fraud¹⁶ by Dr Eric Poehlman who, on his own admission, falsified 17 grant application to the National Institutes of Health and fabricated data in 10 publications. More recently the Lancet retracted a paper on the effect of non-steroidal anti-inflammatory drugs and the risk of oral cancer¹⁷ which was found to contain fabricated material. This finding raised questions about two other papers by the same author in the New England Journal of Medicine in 2001¹⁸ and led to the postponement of a trial on prevention of oral cancer.¹⁹

Research misconduct in the UK

During the last 20-30 years, the United Kingdom has had its fair share of high profile cases of research misconduct^{20, 21}. These predominantly involve employees of Universities and the NHS. Stephen Lock has summarised these cases, many of which were referred to the GMC and some individuals were eventually erased from the Medical Register. Since 1995 the GMC has continued to consider the cases of medical practitioners who have been alleged to have breached accepted standards of research integrity. These inquiries have resulted in the erasure of the gynaecologist Malcolm Pearce, the Edinburgh physician John Anderton, a Professor of respiratory medicine, Robert Davies and a NHS consultant surgeon, Anjan Banerjee¹⁰⁻¹⁵.

The extent of research misconduct

¹⁴ Hwang WS, Ryu Yj, Park JH et al Evidence of a pluripotent human embryonic stem cell line derived from a cloned blastocyst. *Science* 2004; 303(5664): 1669-74.

¹⁵ Hwang WS, Roh SI, Lee BC et al Patient-specific embryonic stem cells derived from human SCNT blastocysts. *Science* 2005; 308 (5729): 1777-83.

¹⁶ Dalton R Obesity expert owns up to million-dollar crime. *Nature* 2005;434:424.

¹⁷ Horton R. Retraction - Non-steroidal anti-inflammatory drugs and the risk of oral cancer; a nested case control study. *Lancet* 2006;367:382.

¹⁸ Curfman GD, Morrisey S, Drazen JM, Expression of concern: Sudbo J et al. DNA content as a prognostic marker in patients with oral leukoplakia. *N Engl J Med* 2001; 344: 1270-8; Sudbo J eto al. The influence of resection and aneuploidy on mortality in oral leukoplakia. *N Engl J Med* 2004; 350: 1405-13.

¹⁹ Couzin J, Schriber M. Fraud upends oral cancer field, casting doubt on prevention trial. *Science* 2006; 311:448-9

²⁰ Lock S. Research misconduct: a résumé of recent events. In, *Fraud and misconduct in medical research*. Ed. S. Lock, F. Wells. 2nd Edition BMJ Publishing Group, London, 1996 pp 14-39.

²¹ Lock s. Research misconduct 1974-1990: an imperfect history. In, *Fraud and misconduct in biomedical research*. 3rd edition. Eds S. Lock, F. Wells, M. Farthing. 2001, pp 51-63

²² Smith R. Misconduct in research: editors respond. *BMJ* 1997;315: 201-202.

²³ Dyer C. Consultant struck off over research fraud. *BMJ* 1997;315:205

²⁴ Wilmshurst P. The code of silence. *Lancet* 1997;349:567-69

²⁵ Ferriman A. Consultant suspended for research fraud. *BMJ* 2000;321:1429

²⁶ Farthing MJG. Retractions in *Gut* 10 years after publication. (Editorial) *Gut* 2001

The true extent of research misconduct in the UK remains unknown. In 1988, Stephen Lock, then editor of the BMJ, published the results of his survey of clinical academics that probed their knowledge of cases of research misconduct²⁷. He concluded that research misconduct was occurring in the UK but was under investigated and largely concealed. In the same period there have been a substantial number of high-profile cases in Scandinavia, France, Germany and in the USA.

Estimates of the extent of research misconduct differ, though some fear that it is widespread and goes undetected^{28,29}. This is supported by subjective data from a questionnaire to the International Society of Clinical Biostatisticians; 51% of respondents said they knew of fraudulent projects³⁰. A third of scientists admitted misconduct in a recent survey³¹. Other surveys reveal that just over 25% of other professionals involved in research are aware of fraudulent projects.

Examples of the impact of research misconduct

High Dose Chemotherapy for Patients With Breast Cancer

In January 2000 doubts emerged about a research project carried out by Dr Werner Bezwoda – a South African oncologist. The South African Medical Research Council was so concerned that it invited a US team of independent research consultants to review a previous study by Dr Bezwoda of High Dose Chemotherapy for patients with breast cancer, which he had presented at a meeting in the US in 1992 and published in 1995. They found that not one of the 90 patients he claimed were part of the study had signed a consent form. Records of nearly 30 of the patients in the trial could not be found and many others not eligible for the study had been included. The review identified three patients that may have died from the HDC treatment even though the publication claimed no deaths occurred. Only seven patients in the study started in 1991 were known to have survived beyond 1995. The results from Dr Bezwoda's cancer trial were recounted in six clinical journals before the fraud was revealed some 5 years after his results were published. The trial results were made public in 1995 at the height of a global debate about the value of high-dose chemotherapy (HDC) for the treatment of breast cancer. This was the first randomised trial to compare HDC with less intensive forms of chemotherapy. After the results were made public many more patients were switched to HDC – especially in the US where the debate on the therapy was intense. Furthermore, up until February 2001 the trial was cited 354 times in other scientific papers. This illustrates the risk to public health world wide when the prescribing practice of medical practitioners is influenced by fabricated evidence.

²⁷ Lock S. Misconduct in medical research: Does it exist in Britain? BMJ 1988; 297: 1531-535.

²⁸ MJ Farthing. Research Misconduct. Gut. 1997;41:1-2

²⁹ A National Panel for Research Integrity: a proposed blueprint for the prevention and investigation of misconduct in biomedical research. Proceedings of the Royal College of Physicians of Edinburgh 2001; 31:253-255

³⁰ Ranstam J, Bayse M, George SL et al For the ISCB Subcommittee on Fraud. Controlled Trials 2000 21(5): 415 – 27

³¹ Martinson BC, Anderson MS, de Vries R. Scientists behaving badly. Nature 2005;435:737-8.

Increased deaths from anti-arrhythmic drugs

In 1980 a group of researchers in Nottingham carried out a study into the drug lorainide – designed to assess the effect of the drug in patients with arrhythmias following a heart attack. Over 90 patients took part in the study; 9 out of the 49 patients given lorainide died during the study. Only one patient receiving a placebo (dummy drug) died. Given the small size of this study, the researchers thought the increased number of deaths among those taking lorainide was due to chance. For a number of reasons the study wasn't published for 13 years. However, during this time other class one antiarrhythmics - continued to be used for patients following a heart attack and it is now estimated that during the 1980s these drugs caused the deaths of between 20,000 and 70,000 people in the US alone every year. The research team involved said that earlier publication 'might have provided an early warning of trouble ahead.'

SMALL COMPANIES ESTIMATED COSTS OF IMPLEMENTING THE CLINICAL TRIALS DIRECTIVE

The ABPI canvassed small businesses as part of their response to the consultation letter on the implementation of the UK Clinical Trials Regulations (MLX 287) and provided estimates of the impact on small businesses that may be typical. They commented that, “whilst there is a basis for the need to charge additional fees it will have a significant impact on smaller companies. For a small company with 2/3 compounds in development these costs are not insignificant”.

Two ABPI smaller member companies provided an estimate of the additional compliance costs likely to incur based on their current clinical trial workload in the UK and that they already work to GCP and GMP standards:

Recurring costs only are summarised. Non-recurring costs such as Manufacturers License, and the costs for ethics review are not included:

Clinical Trials Activity	Estimated cost/year (£)
Fees for clinical trial applications* - 2 CTX's (1 Phase I, 1 Phase II) - 9 Amendments - Annual service charges	3310 900 400
Ethics committees* - 4 submissions - 5 amendments	Unknown at present
Estimated additional contractor QP costs	36,000
Estimated inspection costs/manufacturing licence amendments **	3000

* Based on current experience

** This does not take into account the initial costs contractors may charge for obtaining IMP licences

+ This does not include an estimate for the additional in-house resources required to comply with the implementation of the Directive e.g. annual safety reports

“Commercial” trials activity: Retrospective compliance for 2002 UK activities

Regulatory application	Product 1 (£)	Product 2 (£)	Product 3 (£)
Phase I initial application	-	-	610
Phase II/III initial application unknown IMP	-	-	-
Phase II/III initial application known IMP	2250	-	-
Phase IV initial application	-	-	-
Additional clinical trial protocol authorisation	2 x 100	1 x 100	2 x 100
Other amendments to IMP dossier	4 x 100	-	1 x 100
Annual service charge	200	200	200
GCP inspection (3 yearly) estimated annual cost	5000		
GMP inspection (2 yearly) estimated annual cost	3000		
Total projected annual cost	£12,460		

“Non-Commercial” trials activity: Retrospective compliance for 2002 UK activities*

Regulatory application	Product 1 (£)
Phase I initial application	**
Phase II/III initial application unknown IMP	**
Phase II/III initial application known IMP	**
Phase IV initial application	-
Additional clinical trial protocol authorisation	4 x 100
Other amendments to IMP dossier	2 x 100
Annual service charge	**
Total projected annual cost	£600

Transposition Note for Commission Directive 2005/28 laying down principles and guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products

These regulations do what is necessary to implement the Directive, including making consequential changes to domestic legislation to ensure its coherence in the area to which they apply.

Directive			
Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational products for human use, as well the requirements for authorisation of the manufacturing or importation of such products.			
Articles	Objectives	Implementation	Responsibility
2 to 5	To ensure that all clinical trials are designed, conducted, recorded and reported to the same standards of good clinical practice.	<p>Regulation 2(1) and Schedule 1 of the Medicines for Human Use (Clinical Trials) Regulations 2004 (the principal Regulations) define the conditions and principles of good clinical practice (GCP).</p> <p>Regulation 27(3) of the Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 (the amending Regulations) amends Schedule 1 of the principal Regulations so as to ensure that trials must adhere to the principles of GCP set out in the Directive.</p> <p>Regulation 28 of the principal provides that–</p> <ul style="list-style-type: none"> • No person shall conduct a trial or perform the functions of the sponsor of a clinical trial otherwise than in accordance with the conditions and principles of GCP. • The sponsor of a trial has a duty to have in place arrangements to ensure that the conditions and principles of GCP are complied with. <p>Breach of regulation 28 is a criminal offence (regulation 49 of the principal Regulations)</p>	<p>The Regulations are made by the Secretary of State for Health.</p> <p>Responsibility for enforcement rests with the “enforcement authority”, i.e. the Secretary of State in relation to England, the National Assembly for Wales in relation to Wales, the Scottish Ministers in relation to Scotland, and the Department of Health, Social Services and Public Safety in relation to Northern Ireland. In relation to England, Wales and Scotland, the functions of the enforcement authorities are performed by the Medicines and Healthcare products Regulatory Agency.</p>

6.1	To ensure the harmonisation of the procedures to be used by ethics committees.	Paragraph 6(3) of Schedule 2 to the principal Regulations obliges the ethics committees to make standing orders, and adopt standing operating procedures, for the regulation of its proceedings and business.	Regulations made by the Secretary of State for Health. The United Kingdom Ethics Committee Authority (UKECA) established under regulation 5 of the principal Regulations is responsible for monitoring ethics committees in the UK.
6.2	To ensure that ethics committees retain the “essential documents” relating to a trial for three years.	Regulation 28(b) of the amending Regulations amends paragraph 6 of Schedule 2 to the principal Regulations so as to ensure that ethics committees retain all trial documents on which it gives an opinion for three years from the conclusion of the trial or from the date of their opinion if the trial does not proceed.	Regulations made by the Secretary of State for Health. Responsibility for compliance rest with UKECA..
6.3	To ensure effective communication between ethics committees and the licensing authority	<p>Regulation 14 of the amending Regulations inserts regulation 27A in to the Principal Regulations. Regulation 27A enables the sharing of information by the ethics committees and licensing authority where it may assist either party carrying out its functions under the principal Regulations.</p> <p>A Memorandum of Understanding between UKECA (acting through the Central Office for Research Ethics Committees) and the licensing authority (acting through the MHRA) sets out the arrangements for information sharing, including the obligations, between the parties.</p> <p>Regulation 5 of the amending Regulations amends regulation 4 of the principal Regulations so as to ensure that the licensing authority takes on all the functions and responsibilities of competent authority under the Directive.</p>	Regulations made by the Secretary of State for Health. Responsibility for compliance rests with UKECA.

7.	To clarify the provisions on sponsors in Directive 2001/20/EC (the Clinical Trials Directive)	<p>Regulation 3 of the amending Regulations amends regulation 3 of the Principal Regulations to ensure that sponsors are able to delegate their functions under the principal Regulations whilst retaining overall responsibility.</p> <p>No further provision is required as the sponsor and investigator may already be the same person under regulation 3 of the principal Regulations.</p>	<p>Regulations made by the Secretary of State for Health.</p> <p>Responsibility for compliance rests with the enforcement authority.</p>
8	To provide detail on the investigator's brochure	<p>Regulation 4 of the amending Regulations amends the principal Regulations by inserting a new regulation 3A. Regulation 3A of the principal Regulations sets out the requirements for the investigator's brochure placed on the sponsor.</p> <p>Regulation 9(a) of the amending Regulations amends regulation 15(e) of the principal Regulation to ensure that the Summary of Products can be substituted for the investigator's brochure where the investigational medicinal product has a marketing authorization.</p>	<p>Regulations made by the Secretary of State for Health</p> <p>Responsibility for compliance rests with the enforcement authority.</p>
9	To clarify the circumstances in which a manufacturing authorisation is required	This has been implemented by regulations 36 and 37 of the principal Regulations.	<p>Regulations made by the Secretary of State for Health</p> <p>Responsibility for granting manufacturing authorisations rests with the licensing authority.</p>
10	To set minimum requirements for obtaining a manufacturing authorisation for an investigational medicinal product	<p>Reg 40 of the principal Regulations set out the requirements which must be met before a manufacturing authorisation can be granted (including compliance with regulation 38).</p> <p>Regulation 38 of the principal Regulations requires that an application for a manufacturing authorisation must be in writing and accompanied by the particulars specified in Schedule 6 to the</p>	<p>Regulations made by the Secretary of State for Health</p> <p>Responsibility for granting manufacturing authorisations rests with the licensing authority</p>

		<p>principal Regulations.</p> <p>Schedule 6 to the principal Regulations sets out the particulars that must accompany an application for a manufacturing authorisation.</p> <p>Regulations 21 and 31 of the amending Regulations amend regulation 40 and Schedule 6 respectively so as to ensure that the pharmaceutical form and, where the application relates to the inactivation of viral or non-conventional agents, the manufacturing processes are specified in the application.</p>	
11	To ensure that all applications for manufacturing authorisations are comprehensively and timeously assessed.	This has been implemented through regulations 39 and 40(1)(b) of the principal Regulations.	<p>Regulations made by the Secretary of State for Health</p> <p>Responsibility for granting manufacturing authorisations rests with the licensing authority</p>
12.1	To enable conditional manufacturing authorisations to be granted.	This has been implemented by regulation 40(3) of the principal Regulations.	<p>Regulations made by the Secretary of State for Health</p> <p>Responsibility for granting manufacturing authorisations rests with the licensing authority</p>
12.2	To ensure that applications are specific to products types / forms and premises.	<p>This has been implemented by regulation 41(a) & (c) of, and paragraph 2 of Schedule 6 to, the principal Regulations.</p> <p>Regulation 31(a) of the amending Regulations amends paragraph 2 of Schedule 6 to the principal Regulations.</p>	<p>Regulations made by the Secretary of State for Health</p> <p>Responsibility for granting manufacturing authorisations rests with the licensing authority</p>

13	To ensure holders of manufacturing authorisations meet certain minimum requirements	<p>(a) Implemented by regulation 40(1)(a) of the principal Regulations as amended by regulation 20 of the amending Regulations.</p> <p>(b) Specific provision to implement is not necessary as the disposal of medicines is covered by existing legislation and systems.</p> <p>(c) Implemented by regulation 44 of the principal Regulations as amended by regulation 23 of the amending Regulations.</p> <p>(d) to (f) Implemented by regulation 42 of the principal Regulations as amended by regulation 22 of the amending Regulations.</p>	<p>Regulations made by the Secretary of State for Health</p> <p>Responsibility for granting manufacturing authorisations rests with the licensing authority</p>
14	To impose time restraints on time taken by the licensing authority to consider applications to vary certain key detail of the manufacturing authorisation.	This is implemented by regulation 44(2)(a) of the principal Regulations as amended by regulation 23(a) of the amending Regulations.	<p>Regulations made by the Secretary of State for Health</p> <p>Responsibility for applications to varying manufacturing authorisations rests with the licensing authority</p>
15	To ensure that a manufacturing authorisations shall not continue if the holder does not comply with the relevant requirements.	This has been implemented through regulation 45(1) of the principal Regulations.	<p>Regulations made by the Secretary of State for Health</p> <p>Responsibility for ensuring compliance rests with the enforcement authority</p>
16	To provide further details about the requirements relating to the trial master file and essential documents.	Regulation 18 of the amending Regulations inserts regulation 31A in to the principal Regulations. Regulation 31A(1)-(5) implement this provision.	<p>Regulations made by the Secretary of State for Health</p> <p>Responsibility for ensuring compliance rests with the enforcement authority</p>
17, 19 to 20	To ensure that essential documents are appropriately retained and archived.	Regulation 18 of the amending Regulations inserts regulation 31A in to the principal Regulations. Regulation 31A(6) to (9) implement these provisions.	<p>Regulations made by the Secretary of State for Health</p> <p>Responsibility for ensuring compliance rests with the enforcement authority</p>

18	To ensure the changes in the ownership of trial documents or data are documented and that responsibility also transfers.	Regulation 18 of the amending Regulations inserts regulation 31A in to the principal Regulations. Regulation 31A(10) implements this provision.	Regulations made by the Secretary of State for Health Responsibility for ensuring compliance rests with the enforcement authority
21	To ensure that inspectors are appropriately educated, trained and informed to be able to carry out inspection of clinical trials effectively.	<p>Regulation 4 of the principal Regulations, as amended by regulation 5 of the amending Regulations, provides for the licensing authority to perform the functions of the Member State under the Directive save where those functions are conferred to another body or person</p> <p>Regulation 47 of the principal Regulations confers the enforcement function on the “enforcement authority” by applying sections 108 to 110 of the Medicines Act 1968 to the principal Regulations.</p> <p>Accordingly, the “enforcement authority” is responsible for carrying out the functions of the Directive in relation to enforcement, including matters relating to inspectors.</p>	Regulations made by the Secretary of State for Health Responsibility for the enforcement rests with the enforcement authority.

22	To ensure presence of appropriate skills necessary to certain inspections.	<p>Regulation 4 of the principal Regulations, as amended by regulation 5 of the amending Regulations, provides for the licensing authority to perform the functions of the Member State under the Directive save where those functions are conferred to another body or person</p> <p>Regulation 47 of the principal Regulations confers the enforcement function on the “enforcement authority” by applying sections 108 to 110 of the Medicines Act 1968 to the principal Regulations (with the modifications set out in Schedule 9).</p> <p>Accordingly, the “enforcement authority” is responsible for carrying out the functions of the Directive in relation to enforcement, including matters relating to inspectors.</p>	<p>Regulations made by the Secretary of State for Health</p> <p>Responsibility rests with the enforcement authority</p>
23 to 29	To ensure that GCP inspections follow Community guidelines, work to set procedures, have a legal and administrative framework and are sufficiently resourced.	<p>Regulation 4 of the principal Regulations, as amended by regulation 5 of the amending Regulations, provides for the licensing authority to perform the functions of the Member State under the Directive save where those functions are conferred to another body or person</p> <p>Regulation 47 of the principal Regulations confers the enforcement function on the “enforcement authority” by applying sections 108 to 110 of the Medicines Act 1968 to the principal Regulations (as modified by Schedule 9 of the principal Regulations).</p> <p>Regulations 47 also applies section 111 to 116 of the Medicines Act 1968 to the principal Regulations (as modified by Schedule 9 of the principal Regulations) providing a legal framework for inspections.</p>	<p>Regulations made by the Secretary of State for Health</p> <p>Responsibility rests with the enforcement authority</p>

30	<p>To ensure GCP inspection reports are kept confidential with disclosure limited to the sponsor, other Member States, ethics committees and EMEA.</p>	<p>Regulation 4 of the principal Regulations, as amended by regulation 5 of the amending Regulations, provides for the licensing authority to perform the functions of the Member State under the Directive save where those functions are conferred to another body or person</p> <p>Regulation 47 of the principal Regulations confers the enforcement function on the “enforcement authority” by applying sections 108 to 110 of the Medicines Act 1968 to the principal Regulations (with the modifications set out in Schedule 9).</p> <p>Accordingly, the “enforcement authority” is responsible for carrying out the functions of the Directive in relation to enforcement, including matters relating to inspection reports.</p>	<p>Regulations made by the Secretary of State for Health</p> <p>Responsibility rests with the enforcement authority</p>
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