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GCP INSPECTORS WORKING GROUP

FINAL

REFLECTION PAPER ON ADVICE TO APPLICANTS/SPONSORS/ CROS OF BIOEQUIVALENCE STUDIES

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1. INTRODUCTION

The Marketing Authorisation Application dossier for a generic medicinal product relies on the clinical study report of a single or small number of bioequivalence studies. The validity of the clinical study conduct both in the clinic and in the analytical laboratory is key to the authorisation of the generic product.

The nature of the development and marketing of generic medicinal products means that the oversight of the conduct of these clinical studies faces some specific challenges due to the multiple parties involved at different stages.

The bioequivalence studies are most often conducted by CROs (contract research organisations), many of them specialising in this kind of study. The clinical and analytical laboratory may be the same or different locations and/or organisations. The sponsor of the clinical trial is in some cases the applicant for marketing authorisation. However, in many cases the applicant will have purchased the rights to market a particular generic product from another party and received the technical documentation to support the marketing authorisation application as part of that purchase. The applicant in that case has most likely had no involvement in the conduct and reporting of the bioequivalence study. The applicant does however have an obligation to provide valid data and reports as part of any marketing application made.

The responsibility for the quality and safety of clinical trial data lies with the applicant, sponsors and CROs.

This advisory document has been developed in order to underline the responsibilities of the parties involved, clarify expectations, and reinforce the steps taken by the applicants, sponsors and CROs themselves to ensure the quality of bioequivalence trials submitted in marketing authorisation dossiers.

2. SCOPE and CONTENT

This document is addressed to sponsors, CROs and applicants, specifically in the field of generics. The aim of this document is to increase awareness with the responsible parties that the data submitted in a MA should be of high quality, address safety issues and should be verifiable and to give guidance to the applicant on how to obtain more certainty on the trial data.

Although the authorities assess the quality and content of the MAA dossier, it is the applicant who is ultimately responsible for the quality of the MAA dossier. In the field of generics one study is often used in many MAs, by different applicants in the same or different countries. These studies have been contracted by the sponsor to a CRO and/or specialised laboratories. The applicant is often not the sponsor, and several different applicants may use the same clinical trial/product, in one or more countries.

The quality and safety issues related to the activities of the CRO and specialised laboratories have been described in the Annex 9 of the WHO Technical Report Series, No. 937, 2006, entitled "Additional guidance for organizations performing in vivo bioequivalence studies"[10], which is already very comprehensive for this environment. Therefore the present document refers sponsors, CROs and laboratories as well as applicants to the WHO document, which is available on the WHO website.

The requirements and responsibilities of the sponsor and applicant have not been extensively described in the WHO document and therefore, the present document and advice is directed at aspects that may be verified by and activities that may be undertaken by the applicant and sponsor to ensure the quality of the clinical study data.

3. LEGAL BASIS

General requirements for clinical trials submitted in Marketing Authorisation Applications are set out in Annex I to Directive 2001/83/EC as amended by Directive 2003/63/EC[1]. It should also be noted that all clinical trials conducted in third countries should be conducted to the ethical standards of Directive 2001/20/EC[2] and the applicant will have to testify to this when submitting a marketing authorisation using the clinical trial.

In addition to the legal context, there are already a number of guidelines and documents available that are applicable to the clinical trial environment, including the CPMP/ICH/135/95 Note for guidance on Good Clinical Practice[3] and the CPMP/EWP/QWP/1401/98 Note for guidance on the investigation of bioavailability and bioequivalence[4]. This document will therefore only cover those aspects where additional information may be helpful

4. POINTS TO CONSIDER

A: Data Verification & Quality

A number of guidance documents are available to enhance the quality and safety of clinical trials.

For the clinical part of the studies:

CPMP/ICH/135/95[3], Declaration of Helsinki[5], other CHMP/ICH-Guidelines[6]

For the bioanalytical part

CPMP/ICH/135/95[3], CPMP/EWP/QWP/1401/98[4], GLP[7, 8] *

For the PK and statistical analysis

CPMP/ICH/135/95[3], CPMP/EWP/QWP/1401/98[4]

Reference should also be made to other applicable CHMP/ICH-Guidelines that may be applicable in that context.

* The CPMP/EWP/QWP/1401/98 Note for guidance on the investigation of bioavailability and bioequivalence states "The bio-analytical part of bioequivalence trials should be conducted according to the applicable principles of Good Laboratory Practice." The sites conducting these studies and the studies themselves do not fall under the GLP legislation per se. The sites are not required to be certified as part of the GLP compliance certification scheme.

B: CRO, Sponsor, Applicant

Refer, also, to section 7 – Specific activities of the applicant and to section 8 – Specific activities of the sponsor

For evaluation of quality the following aspects are relevant:

- type of organisation and its activities, other MA dossiers that have used data from these sites/organisations, previous inspection experience etc...
- qualification of the facilities where the studies are performed
- availability of audit certificates,
- documentation on delegation of activities where applicable

C: Investigational Medicinal product

In addition to the legal obligations a number of additional guidance documents is available that need to be followed to ensure optimal quality of the investigational product (reference and comparator).

Quality of the IMP: Chapter III of the EUDRALEX Volume 10- Clinical trials (Information on the Quality of the Investigational Medicinal Product) [9]

Further aspects that need to be taken into account are:

- type of product (e.g. stability, PK and PD profiles, and analytical methods)
- production site (e.g. location, GMP license/inspection, QP activities)
- traceability
- conditions of administration of the product-
- provision of in vitro dissolution data for both test and reference products

D: Biological samples

Labelling, traceability, storage and transport conditions of the biological samples before their analysis should be considered.

E: Regulatory & Ethical Issues

- location of sponsor, CRO, clinical and laboratory sites (e.g. already well known region/regulatory environment) the location/regulatory environment, (EU/EEA, third countries) of the clinical and laboratory sites,
- subjects (e.g. type, group, patients or volunteers, vulnerable populations)
- Ethics Committee and Competent Authority (e.g. applicable local regulations and guidelines, national, international, trial type, specific local guidance).

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5. ADMINISTRATIVE ACTIVITIES

As many studies are either contracted to third parties or bought from other parties, close attention should be paid to the content of the contracts, to ensure that quality elements are clearly described.

- contracts should include provisions concerning study quality, verification issues, access to all the original data and processes, and archiving aspects.
- quality evaluation of the contract partner or of the acquisition of the dossiers should be a standard part of the negotiations for buying or contracting.
- processes and systems used in the development of the clinical data should be clearly described and verifiable.
- quality assurance processes such as monitoring and auditing of the study sites, processes and data should be evaluated.
- there should be transparency of all transactions for the involved parties.
- the transactions should include specific undertakings for GCP/GMP compliance and compliance with other relevant guidance including applicable GLP principles, legal obligations, and Note for guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98). This can be formalised on the basis of audit and monitoring reports related to the quality of the site and data.

6. SPECIFIC ACTIVITIES OF THE SPONSOR:

At the time of contracting a study to a CRO, the sponsor should consider the following activities:

- preferred vendor audits
- facilities and procedures of CRO
- evaluation of the responsibilities of the sponsor and the CRO
- quality and completeness of the protocol
- validation of analytical methods
- validation of clinical activities
- IMP manufacturing and packaging.
- qualifications of personnel (e.g. investigators, technicians, monitors)
- quality system (including performance of monitoring and auditing) implemented by the CRO and the sponsor
- definition of tasks and responsibilities in contracts between CRO and sponsor
- performance of audits by the sponsor (pre-contracting, post-contracting); evaluation of audit results and improvement cycles
- verification of archiving of source data
- provisions and procedures to apply in the event of non-compliance, by the CRO or the sponsor, with regulatory requirements

At the time the study is finalised by a CRO the following activities may be undertaken by the sponsor:

- verification of report, data listings, statistics and protocol
- effectiveness of contracted responsibilities
- performance of audits by sponsor (post-study); Evaluation of audit results and improvement cycles
- verification of (continued) archiving source data

7. SPECIFIC ACTIVITIES OF THE APPLICANT

At the time of buying or developing an application dossier the applicant should consider the following activities:

- quality requirements detailed in contracts (safeguards to apply when purchasing a dossier)
- verification that the sponsor/CRO had adequate control of the quality of the study (performance and outcome of sponsor audits; evaluation of the activities of the sponsor)
- general information on the CRO and their procedures
- verification of contracts between sponsor and CRO (details on quality, tasks included in contracts)
- audit of the clinical and bio analytical sites
- in relation to IMP production, verification of GMP certification, inspection status (and site authorisation where applicable) and audit

- verification and guarantees of continued archiving and availability of source data
- provisions and procedures to apply in the event of non-compliance, by the CRO or the sponsor, with regulatory requirements

8. GENERAL CONCLUSION

A quality system approach to the sponsoring, contracting, purchase of a dossier/product or applying for a marketing authorisation will give a good basis through which verification of a number of the above issues can be implemented. This approach will ensure that the chances for problematic quality in (BA/BE) study dossiers used in generic applications are lessened.

This document should be used as complementary to the legal requirements, existing guidelines, including the CPMP notes for guidance on GCP[3] and on investigation of bioequivalence[4] and the WHO publications[10].

9. REFERENCES

1. Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use (Official Journal L 159, 27/6/2003 p. 46 - 94)
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2003_63/dir_2003_63_en.pdf

2. 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 (*Official Journal L 121, 1/5/2001 p. 34 - 44*).
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf

3. CPMP/ICH/135/95 Note for guidance on Good Clinical Practice (ICH E6)
http://www.emea.eu.int/pdfs/human/ich/013595en.pdf

4. CPMP/EWP/QWP/1401/98 revised 26 July 2001 Note for guidance on the investigation of bioavailability and bioequivalence –http://www.emea.eu.int/pdfs/human/ewp/140198en.pdf

5. Declaration of Helsinki - http://www.wma.net/e/policy/b3.htm

6. Other CPMP/ICH-Guidelines

- CPMP/ICH/381/95 Validation of Analytical Procedures: Text and Methodology (ICH Q2(R1)) http://www.emea.europa.eu/pdfs/human/ich/038195en.pdf
- CPMP/ICH/137/95 Structure and Content of Clinical Study Reports (ICH E3) http://www.emea.europa.eu/pdfs/human/ich/013795en.pdf

7. OECD Series on Principles of Good Laboratory Practice and Compliance
http://www.oecd.org/findDocument/0,3354,en_2649_34381_1_1_1_1_1,00.html

8. Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances (codified version)

(Official Journal L 050, 20/02/2004 P. 0044 – 0059)
http://eur-lex.europa.eu/LexUriServ/site/en/oj/2004/l_050/l_05020040220en00440059.pdf

9. EUDRALEX Volume 10 - Clinical trials
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev10.htm

10. WHO Technical Report Series, No. 937, 2006. Annex 9, “Additional guidance for organizations performing in vivo bioequivalence studies” (pages 439-461)
http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf

11. EMEA/P/24143/2004 Procedure for European Union guidelines and related documents within the pharmaceutical legislative framework
http://www.emea.eu.int/pdfs/human/regaffair/2414304en.pdf