The European Agency for the Evaluation of Medicinal Products
Human Medicines Evaluation Unit

8 September 1997
CPMP/768/97

Explanatory Note and Comments to the ICH Harmonised Tripartite Guideline E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)

Introduction

Having reached Step 4 of the ICH process at the ICH Steering Committee meeting on 1 May 1996, the ICH Guideline for Good Clinical Practice was recommended for adoption to the three regulatory parties to ICH. In the EU, final approval by the CPMP of the EMEA occurred on 17 July 1997 (CPMP/ICH/135/95), in Japan the ICH GCP guideline was published at the end of March 1997 as part of the "Japanese technical requirements for new drug registration 1997" and is implemented stepwise (last step on 1 April 1998). In the USA the guideline was published and made effective on 9 May 1997 in the Federal Register. To maintain the harmonisation reached in the area of clinical trials, the adherence to the agreed GCP standard is crucial. The mutual acceptance of data and ultimately Mutual Recognition Agreements depend on successful Step 5 in the three ICH regions and the harmonised implementation in these regions.

An inventory of regional differences in Step 5 with impact on the further process is essential to allow for corrective action and a long-term pro-active approach in view of mutual recognition of GCP inspections. An inventory of easily occurring deviations and differences in interpretations is expected to be useful, not only for sponsors, CROs, investigators, ethics committees, but also for regulatory authorities from other countries that would like to take over ICH GCP, or future EU Member States which will adopt the Note for Guidance on GCP (CPMP/ICH/135/95). The overview illustrates how the endeavour for a fast harmonisation process is not without technical hurdles and human errors, but common sense will allow professionals working in the GCP area to differentiate between obvious errors and intentional changes. Regulatory compliance does not depend on a comma or one word but on the overall implementation of the GCP standard. To remain a valuable tool, it is the intention to update the inventory of regional differences regularly.

Step 5 in the EU

The ICH GCP Step 4 document adopted by the ICH Steering Committee got some errata, of which one was known only after the CPMP adopted the guideline. An attempt was made to address the errata in the EU by providing subsequently on the Internet at **http://www.eudra.org/emea.html** the guideline containing most corrections incorporated in the ICH secretariat's Step 4 version. Besides these corrections, 3 changes were made in that version, which were not released by the ICH secretariat and based on an earlier uncorrected version. In the EU, the present electronic version, characterised by the footnote * *including post Step 4 errata*, should be used. This electronic version shows as date for coming into operation 17 January 1997, which means that this guideline should be used for studies

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commencing after 17 January 1997. The fact that the revised GMP Annex 13, adopted on 2 December 1996 by the Working Party on 'Control of Medicinal Products and Inspections' to come in operation on 1 July 1997, states in a Note in the Introduction that the Guideline on Good Clinical Practice is *"revised on 1 January 1997"*, has no impact on the date established by the CPMP. CPMP adopted documents will not show anymore a specific calendar date, but rather a month and year after which compliance is expected.

The legal framework to ensure a harmonised GCP implementation in the EU, and European Economic Area (EEA), is under development and several versions of Draft Directive III/5778/96 have been circulated by Commission Services and were discussed at public meetings.

Step 5 in Japan

For the Japanese translation the English version, including post Step 4 errata, was used and is published in the English compilation of "Japanese Technical Requirements For New Drug Registration 1997", published in March 1997 by the MHW. The official ICH Secretariat's electronic version was used, so users can be confident that this published version is the GCP standard in Japan. Also in the Japanese version, original ICH GCP wordprocessing errors may still be present, as for instance in 8.2.6, where the signed agreement between the sponsor and CRO, of course, does not need to be located in the investigator's file. Consider rather the advantage of having this English compilation. Users of the Japanese translation of the ICH GCP can verify at any time the English original thanks to this compilation. For inspection purposes by foreign authorities the English compilation is also useful.

The legal framework for the stepwise introduction of ICH GCP in Japan is under development. The new law was published and by-laws need to be considered as well. The English version of "Japan's New GCP and Other Rules on Clinical Trials", published on 7 July 1997, was made available to the ICH Steering Committee on the occasion of the ICH4 meeting and contains an informative table with a comparison of the previous Japanese legislation with the new and future one. On 1 April 1997 written informed consent was introduced and the acceptance of monitoring and auditing will go into effect on 1 April 1998.

Step 5 in the USA

The ICH GCP guideline was published in the Federal Register on 9 May 1997 with an electronic version available via Internet at **http://www.fda.gov/cder**. The version is not identical with the ICH Step 4 document. Most changes are without any impact for the users and do not change any of the concepts as discussed and agreed upon within the ICH process. Listed hereunder is changed wording that may have impact and lead to questions from the part of industry. Other differences were not overlooked, but are considered minor and therefore not addressed, since they do not change the sense of the original ICH GCP text. Presenting this annotated comparison is expected to be helpful in the interpretation of the guideline and provides an answer to questions raised by users about the significance of the changes. Since a guideline allows flexibility, users should be confident in using the ICH GCP text developed by GCP industry experts and authority representatives, used to work with a global approach. Important above all in GCP in the three ICH regions is the documented evidence of the adherence to this international ethical and scientific quality standard.

Table 1: Comparison ICH GCP Step 4 with text published in the Federal Register, Vol. 62, No 90, 25691-25709

Paragraph, item	ICH GCP Step 4	Federal Register	Comments
1.4 Applicable Regulatory Requirement(s)	Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products.	Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products **of the jurisdiction where a trial is conducted.**	Additional clarification
1.31 Institutional Review Board (IRB)	... and providing continuing review of trial protocol and amendments ...	... and providing continuing review of **trials, of protocols** and amendments ...	Additional clarification regarding IRB, specific for US, not applicable in the EU
1.52 Source documents	... copies or transcriptions certified after verification as being accurate copies, ...	... copies or transcriptions certified after verification as being accurate **and complete**, ...	The replacement of "copies" by "and complete" does not change the concept
3.4 Records	The IRB/IEC may be asked by investigators, sponsors or regulatory authorities to provide its written procedures and membership lists.	The IRB/IEC may be asked by investigators, sponsors or regulatory authorities to provide **copies of** its written procedures and membership lists.	Clarification that copies were meant
4.10 Progress Reports 4.10.1	The investigator should submit written summaries of the trial status to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.	**Where required by the applicable regulatory requirements, the investigator should submit written summaries of the trial status to the institution.** The investigator/institution should submit written summaries of the trial status to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.	**NEW addition to Step 4 text**. The supplementary information provided in the Fed. Register does not indicate that the published text differs from the Step 4 ICH GCP. It only mentions that comments in the docket will be periodically reviewed, and, where appropriate, the guideline will be amended. **The public will be notified of any such amend-ments through a notice in the Federal Register. This is not the case for the present amendments.**
4.10.2	The investigator should promptly provide written reports to the sponsor, the IRB/IEC (see 3.3.8), and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.	The investigator should promptly provide written reports to the sponsor, the IRB/IEC (see 3.3.8), and, where **required by the applicable regulatory requirements**, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.	**The original "where applicable" did not stand for applicable regulatory requirements only, but considered the eventual institutional or IRB/IEC procedures.** Users of the US version of ICH GCP should be aware that in the EU and Japan 4.10.2 is also applicable if it is a requirement for a particular trial site. *
	... the investigator should inform the institution where applicable, and ...	the investigator should inform the institution where **required by the applicable regulatory requirements**, and	**The original "where applic-able" did not stand for appli-cable regulatory requirements only, but considered the eventual institutional or IRB/IEC procedures**. Users of the US version of ICH GCP should be aware that in the EU and Japan 4.12.1 is also applicable if it is a requirement for a particular trial site. *

* Since the ICH sponsors are industry and authorities it could be for that reason that requirements from the part of the institution and/or IRB/IEC related to investigator's duties were not appropriate and therefore changed. However this is valid for all requests from the IRB/IEC and elsewhere in the document published in the Fed. Register such changes were not made.

Table 1: Comparison ICH GCP Step 4 with text published in the Federal Register, Vol. 62, No 90, 25691-25709 (continued)

Paragraph, item	ICH GCP Step 4	Federal Register	Comments
4.12.2	... the investigator should promptly inform the institution where applicable, and ...	... the investigator should promptly inform the institution where **required by the applicable regulatory requirements**, and ...	**The original "where applicable" did not stand for applicable regulatory requirements only, but considered the eventual institutional or IRB/IEC procedures.** Users of the US version of ICH GCP should be aware that in the EU and Japan 4.12.2 is also applicable if it is a requirement for a particular trial site. *
4.13	Upon completion of the trial, the investigator, where applicable, should inform the institution; ...	Upon completion of the trial, the investigator, where **required by the applicable regulatory requirements,** should inform the institution; ...	**The original "where applicable" did not stand for applicable regulatory requirements only, but considered the eventual institutional or IRB/IEC procedures.** Users of the US version of ICH GCP should be aware that in the EU and Japan 4.12.2 is also applicable if it is a requirement for a particular trial site. *
5.18.4 (k)	Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained.	Verifying that source **data**/documents and other trial records are accurate, complete, kept up-to-date and maintained.	ICH GCP definition of source documents contained already "data", so addition has no impact
5.19.2 (a)	The sponsor should appoint individuals who are independent of the clinical trials/systems, to conduct audits.	The sponsor should appoint individuals who are independent of the clinical trials/data collection systems, to conduct audits	Addition to Step 4 document, which may be considered as a reinforcement of the independence of the auditor(s) and the fact that they perform systems audits. However it seems to limit this to data collection systems, excluding data analysis, report writing, etc. which was not the intention of the ICH GCP experts.
5.19.3 (d)	Regulatory authority (ies) may seek access to an audit report on a case by case basis when evidence of serious GCP non-compliance exists, or in the course of legal proceedings.	Regulatory authority (ies) may seek access to an audit report on a case by case basis when evidence of serious GCP non-compliance exists, or in the course of legal proceedings **or investigations**.	Addition to clarify that audit reports can be requested to examine facts and not only at the time a lawcourt or other official body is used to settle the case. In fact as a result of the investigation it may not be a case for the court.
8.4.4	Audit certificate (if available). To document that audit was performed	Audit certificate (if **required**). To document that audit was performed **(if required)(see 5.19.3 (e))**	In the Step 4 document the EU Directive 91/507/EEC expression "if available" was kept. **The change makes it clear that in an explicit way the applicable law or regulation should require it.** The ICH guideline on the Structure and Content of Clinical Study Reports also keeps the expression "if available". "If available" depends in the EU on whether an audit was conducted or not until now (selfregulation by industry) not because it is "required".

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