CHAPTER 1

Good Clinical Practice Principles: Legal Background and Applicability

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SUMMARY

Since 1991 the European Medicines Agency (EMA, formerly EMEA) adopted the Guidelines of the International Conference on Harmonization (ICH) on Good Clinical Practice (GCP). In this regard, one European Union (EU) Guideline and three EU Directives are in force at present, that is, the E6/CPMP/ICH/135/95 GCP Guideline, Directive 2001/83/EC (Community Codex on Pharmaceuticals), Directive 2001/20/EC (GCP and Clinical Trials, CTs), and Directive 2005/28/EC (Detailed Guidance on GCP).

European Directive 2001/20 on GCP and CTs has been widely criticized by a large portion of the scientific community more directly involved in the promotion and management of noncommercial academic CTs. Since 2003 several scientists from academia highlighted through the international scientific literature the difficulties inherent in the new EU regulation, in particular as regards GCP compliance and quality monitoring problems. Such difficulties have also been acknowledged by Directive 2005/28 where, among others, it is stated that for academic CTs the application of certain GCP aspects may be unnecessary or guaranteed by other means.

None of these documents oblige CTs to be in compliance with the GCP ICH Guideline (GCP-ICH) full text and details. Rather, they prescribe that CTs be in compliance only with GCP principles and with GCP Guidelines laid down in Directive 2005/28 EC, this being less binding when compared to the GCP-ICH Guideline. At the national level, EU Member States (MS) adopted different legislation to implement the GCP obligations. MS GCP Inspectorates generally act as if all GCP aspects were mandatory to verify the reliability of data reported by the CTs audited.

At the international level, in particular in developing countries, where several bioequivalence (BE) studies are conducted and the number of CTs is increasing, often

Analytical Techniques for Clinical Chemistry: Methods and Applications, First Edition.
Edited by Sergio Caroli and Gyula Záray.

neither specific aspects nor the principles of GCP are complied with. In the case of data submitted to EU MS Regulatory Authorities (RAs) for a Marketing Authorization (MA) of a medicinal product, the CTs of which were performed outside the EU, Directive 2001/83 allows the MA to be granted only if the CTs are in compliance with the ethical principles of GCP, although in practice only a few RAs assess that this actually has been done.

Specific examples are given to illustrate the above issues and a number of key aspects related to laboratory activities are reported and discussed in the frame of different international normative and guidelines on GCP.

1.1. INTRODUCTION

Since 1991 the European Medicines Agency (EMA, formerly EMEA)[1] adopted the Guidelines of the International Conference on Harmonization (ICH) on Good Clinical Practice (GCP). In this regard, one European Union (EU) Guideline and three EU Directives are in force at present, that is, the E6/CPMP/ICH/135/95 GCP Guideline [1], Directive 2001/83/EC (Community Codex on Pharmaceuticals) [2], Directive 2001/20/EC (GCP and Clinical Trials, CTs) [3], and Directive 2005/28/EC (Detailed Guidance on GCP) [4].

The introduction of GCP in EU is linked with Good Manufacturing Practice (GMP), particularly Annex 1, 13, and 16 (*The rules governing medicinal products in the European Union*, EudraLex, Vol. 4) [5] regarding directly or indirectly the production of Investigational Medicinal Product (IMP) and Directive 2003/94/EC on GMP for Medicinal Products and IMP [6]. At global level, besides ICH-GCP, WHO has also issued WHO GCP.

The GCP legal background and applicability are discussed hereafter along with the description of related documents and implementation problems. This legal framework is of paramount importance to attach credibility to the experimental information obtained when carrying out clinical investigations, thus substantially contributing to preserving and improving human health.

1.2. GOOD CLINICAL PRACTICE

1.2.1. ICH E6: Guidelines for Good Clinical Practice

ICH Guidelines for GCP [1] have been prepared by the ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use, which is composed by the Medicine Regulatory Agencies and members of the pharmaceutical industry of the EU, Japan, and the USA. The WHO, Canada, and European Parliamentary Technology Assessment (EPTA) have observer status. Since its creation in 1990, the ICH has issued 58 Tripartite Guidelines on issues related to its four main areas of work, namely quality, safety, efficacy, and multidisciplinary topics. The process to

[1] After the completion of this chapter the European Medicines Agency changed its acronym from EMEA to EMA.

reach harmonization of technical requirements resulting from scientific progress goes along with the process of keeping up-to-date the current guidelines, in order to ensure that the harmonization process, so far achieved, is not lost. Guidelines are adopted by the Steering Committee and signed by the three regulatory parties to ICH. However, guidelines become binding only when the regulatory bodies in the three regions implement them. The objective of this guidance is to provide "*international ethical and scientific quality standards for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible*."

ICH E6 GCP Guideline is designed to set a unified standard for the ICH countries in order to facilitate the mutual acceptance of clinical data by RAs in these jurisdictions and speed up registration for market authorization of medicines. Topics covered include the composition of Ethics Committees/review boards, the responsibilities of investigators and sponsors, provisions regarding trial protocols and protocol amendments, including treatment of data, informed consent, payment of subjects, insurance in case of harm. This guideline has been adopted by the EU in 1995 (updated version) [1] and largely transposed into their legislation by the United States [7] and Japan in 1997.

ICH Good Clinical Practice Principles

The ICH-GCP Principles can be divided into three different categories:

(a) Principles to guarantee the "ethical aspects" of the CT, as follows.
- CTs should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP and the applicable regulatory requirements.
- The rights, safety, and well being of trial subjects are the most important considerations and should prevail over interests of science and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
- Freely given informed consent should be obtained from every subject prior to CT participation.

(b) Principles to guarantee the "technical-scientific aspects" of CT, namely.
- The available nonclinical and clinical information on an investigational product should be adequate to support the proposed CT.
- The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
- Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his/her respective task(s).
- Investigational products should be manufactured, handled, and stored in accordance with applicable Principles of GMP. They should be used in accordance with the approved protocol.

(c) Principles to guarantee the "quality and procedural aspects" of CT.

- All CT information should be recorded, handled, and stored in a way that allows for its accurate reporting, interpretation, and verification.
- The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirements.
- CTs should be scientifically sound and described in a clear, detailed protocol.
- A trial should be conducted in compliance with the protocol that has received prior Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval/favorable opinion.
- Systems with procedures that assure the quality aspects of the trial should be implemented.

GCP Details in the Field of the Quality

ICH-GCP Guidelines describe in detail how the principles can be implemented. Principles related to the quality of the CT are crucial for all clinical investigations. Many paragraphs of GCP are related to quality principles. Among others, the following should be noted.

- *The investigator/institution should maintain the trial documents as specified in "Essential Documents for the Conduct of a Clinical Trial" and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents (par. 4.9.4).*
- *The sponsor is responsible for implementing and maintaining Quality Assurance (QA) and Quality Control (QC) systems with written Standard Operating Procedures (SOPs) to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s) (par. 5.1.1).*
- *QC should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly (par. 5.1.3).*
- *If significant formulation changes are made in the investigational or comparator product(s) during the course of clinical development, the results of any additional studies of the formulated product(s) (e.g., stability, dissolution rate, bioavailability) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the product should be available prior to the use of the new formulation in clinical trials (par. 5.13.5).*
- *The sponsor should*
  (a) *take steps to ensure that the investigational product(s) are stable over the period of use;*
  (b) *maintain sufficient quantities of the investigational product(s) used in the trials to reconfirm specifications, should this become necessary, and maintain records of batch sample analyses and characteristics. To the extent stability permits, samples should be retained either until the analyses of the*

trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period (par. 5.14.5).

- *To document normal values and/or ranges of the tests the following documents must be maintained: Normal Value(s)/Range(s) for Medical/Laboratory/Technical procedure(s) and/or test(s) included in the protocol (par. 8.2.17).*
- *To document competence of facility to perform required test(s), and support reliability of results, the following documents must be maintained regarding Laboratory/Technical procedures/Tests: certification or accreditations or established QC and/or external QA or other validation (where required) (par. 8.2.12).*

1.2.2. WHO Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products

These guidelines [8] have been prepared by the WHO, in consultation with National Drug Regulatory Agencies in developed countries. It is intended to set globally accepted and applicable standards for the conduct of trials with human subjects by bringing together standards already in use in developed countries. Their aim is to provide mutual recognition of data among interested countries and contribute to the process of harmonization of provisions. It is interesting to note that while the guidelines do not challenge or replace national guidelines, they aim at being a model for standard setting in those countries where no regulation exists.

The guidelines are designed to be applicable to all stages of drug development, but they can be applied to biomedical research as a whole, including evaluation of scientific and ethical integrity of manuscripts submitted to editors for publication.

Principles and detail of WHO GCP are similar to those of ICH-GCP.

1.2.3. WHO Handbook for Good Clinical Research Practice Guidance for Implementation

This document [9] is an adjunct to WHO's Guidelines for GCP for trials on pharmaceutical products (1995) [8]. The handbook aims at assisting national RAs, sponsors, investigators, and Ethics Committees in implementing GCP for industry-sponsored, government-sponsored, institution-sponsored, or investigator-initiated clinical research.

1.2.4. WHO Good Clinical Laboratory Practice

This guidance [10] identifies systems required and procedures to be followed within an organization conducting analysis of samples from clinical trials in compliance with the requirements of GCP. It thus provides sponsors, laboratory management, project managers, Clinical Research Associates (CRAs), and QA personnel with the framework for a quality system in analysis of clinical trial samples, ensuring GCP thorough compliance processes and results.

The Special Program for Research and Training in Tropical Diseases (TDR) Diagnostics Evaluation Expert Panel (DEEP) has recommended GCLP as the standard for clinical laboratories involved in the evaluation of diagnostics for infectious diseases.

This document is intended to provide a framework for the analysis of samples from clinical trials on the facilities, systems, and procedures that should be present to assure the reliability, quality, and integrity of the work and results generated by their contribution to a clinical trial.

It is recommended that the framework outlined in this document be adopted by any organization that analyzes samples generated by a clinical trial.

The principles defined in this framework are intended to be applied equally to the analysis of a blood sample for routine safety screening of volunteers (hematology/biochemistry) as to pharmacokinetics or even the process for the analysis of ECG traces.

The types of facilities undertaking analyses of clinical samples may include pharmaceutical company laboratories, Contract Research Organisations (CROs), central laboratories, pharmacogenetic laboratories, hospital laboratories, clinics, investigator sites, and specialized analytical services.

GCLP applies those Principles established under GLP for data generation used in regulatory submissions relevant to the analysis of samples from a clinical trial. At the same time it ensures that the objectives of the GCP Principles are achieved. This ensures the reliability and integrity of data generated by analytical laboratories.

This guidance provides details, among others, on the following issues: personnel responsibilities; facilities; equipment, materials, and reagents; SOPs; trial materials; conduct of the work; QC; quality audit.

1.3. GOOD CLINICAL PRACTICE: LEGAL BACKGROUND IN THE EUROPEAN UNION

In the EU, ICH-GCP Guidelines have been adopted by the Committee for Proprietary Medicinal Products (CPMP) of the EMA in 1991 and at a later stage as the updated version of 1996 [1].

The EMA Guidelines are not mandatory, but many aspects of GCP have been introduced in EU Directives, namely Directive 2001/20/EC of the European Parliament and of the Council of April 4, 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* [3] and 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* [4].

The main provision of these two Directives is that all CTs, including bioavailability (BA) and bioequivalence (BE) studies, shall be designed, conducted, and reported in accordance with the principles of GCP. Other targets of CT Directives are as follows:

- simplification and harmonization of CTs across the EU;
- better protection of subjects who take part in CTs;
- enforcement by law of the principles of GCP and GMP.

The scope of the CT Directives is wide. It covers all commercial and academic CTs of IMPs and marketed medicines.

The types of IMPs specified in the Directive 2005/28/EC (5) are the following:

- chemical entities;
- biotechnology products;
- cell therapy products;
- gene therapy products;
- plasma-derived products;
- other extractive products;
- immunological products, such as vaccines, allergens, and immune sera;
- herbal products;
- homeopathic products;
- radiopharmaceutical products.

Also a placebo, or a marketed product used or assembled in a way other than the approved form, is an IMP when used as a comparator.

The impact of the CTs Directive on trials is as follows:

- the already mentioned obligation is to be in compliance with the ICH-GCP principles;
- trials of IMPs in healthy subjects and in patients are regulated in all EU Member States (MSs) according to CT Directives;
- sponsors must apply to and receive approval from the national RA for a Clinical Trial Authorization (CTA) and for substantial protocol amendments;
- investigators must apply to and receive approval from Ethics Committee for the protocol and substantial amendments.

According to this legislation Ethics Committee foreseen in ICH-GCP are in charge of supervising CTs. Ethics Committee is *an independent body in a MS whose responsibility it is to protect the rights, safety and well being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, and on the methods and documents to be used to inform trial subjects and obtain their informed consent (article 2 (k) of Directive 2001/20/EC* [3]*).*

The Ethics Committee approval is necessary before the commencement of a clinical trail. The Ethics Committee shall consider, among other things, also aspects regarding quality of the trial such as

(1) the relevance of the CT and the trial design;
(2) the protocol;
(3) the suitability of the investigator and supporting staff; and
(4) the quality of the facilities.

To verify compliance with the provisions on GCP, EU MS appoint inspectors to inspect the sites concerned by any CT conducted, particularly the trial site, the sponsors, premises, and Ethics Committee as well.

The inspections shall be conducted on behalf of the EU and the results shall be accepted by all EU MSs.

1.4. GOOD CLINICAL PRACTICE: APPLICABILITY IN THE EUROPEAN UNION

1.4.1. EU 2007 Conference on the Implementation and Applicability in the European Union of Legislation on Clinical Trials of Medical Products

At the request of the European Commission (EC), the EMA organized on October 30, 2007 a conference on the implementation and applicability in the EU of legislation on CTs of medicinal products and on GCP-related Guidelines.

It was recognized by conference participants that the legislation on CTs has introduced a common legal framework and a legal basis for compliance with GCP and has improved the protection of individuals through procedures for ethical approval of CTs in the EU.

Participants stressed the importance of maintaining the general principles of protecting patients, facilitating high-quality research, and promoting a favorable research environment in the EU.

It was acknowledged that, in some cases, problems that have been encountered appeared to be a consequence of different interpretations and different implementation in the national legislation of the MS, whereas other aspects would need to be addressed through proposed changes to the legislation.

The main areas in which efforts should be focused are multinational CTs, safety reporting and monitoring, noncommercial sponsorships/trials, CTA dossier and process, IMP-related issues, and the application of ethical principles and GCP standards in developing countries.

The key issues arising from the conference presentations are summarized below.

Based on data from the European data base on Clinical Trial (EudraCT), 80% of CTs conducted in the EU since 2004 have been by commercial sponsors and 20% by noncommercial sponsors.

Most of the trials are performed in multiple sites and multiple countries. The challenge in the EU is therefore to optimize the regulatory environment to

- ensure protection of subjects participating in CTs (EU and third countries);
- ensure a framework for high-quality research in the EU and its acceptability worldwide (product development, product authorization);
- promote a favorable research environment (clear, efficient, and effective administrative and scientific procedures).

The Directives have set out a legal basis for GCP compliance in the conduct of CTs. As a result, increased awareness of the requirements for the conduct of CTs, including

GCP, has led to improvements in the available infrastructure for clinical-trial management and improved GCP compliance.

The GCP Inspectors Working Group (WG) recommended that there be a harmonized reference to ICH-GCP as the EU standard in the EU legislation.

It was noted that, while requirements for CTs of medicinal products are well regulated and relatively well harmonized, requirements for other biomedical research on human subjects are poorly implemented. It was recommended that both the GCP standards and harmonized administrative requirements should apply not only to CTs with investigational medicinal products but also to other types of trials, including those for *in vitro* diagnostics, medicinal devices, and so on.

As far as commercial and noncommercial trials and sponsors are concerned, consensus was reached on the fact that there should be one set of GCP standards for all trials, and not different standards for commercial trials and for noncommercial trials. Noncommercial investigators, in the authors' view, did not realize that this approach could require in the future the compliance to the full text of GCP provisions, rather than only to principles as it is now. In fact, rather than a distinction between commercial and noncommercial trials, the idea of a differential application of the legislation, using a risk-based approach, was proposed. This approach should be based on the risk involved in the trial and on the extent of knowledge of the product (e.g., novel product, marketed product, marketed product used within its Summary of Product Characteristics (SPC), and so on), thus avoiding the development of double standards in terms of GCP compliance and quality and credibility of data. This approach would prevent the perception that there be two levels of quality in the present legislation and in its implementation. It would lead to a general improvement in the quality and cost effectiveness of trials (e.g., better prioritization of monitoring and of other QC activities).

Proposals to improve the cost-effectiveness of noncommercial trials without reducing compliance with GCP included adapting record-keeping and monitoring requirements (e.g., by web-based trial master files/investigator site files and by developing models of monitoring and auditing tailored to the structures or their organizations and the risk of the trials).

1.4.2. Directives 2001/20/EC, 2005/28/EC, and Good Clinical Practice in Case of Noncommercial Clinical Trials

Aspects of Directives 2001/20 and 2005/28 regarding GCP and noncommercial clinical trial misunderstood by some noncommercial investigators.

European Directive 2001/20 EC on GCP and CTs has been widely criticized by an important part of the scientific community more directly involved in the promotion and management of noncommercial or academic CT. Since 2003 several academic experimentalists stressed on scientific international literature difficulties derived from new EU Regulation specifically as far as it concerns: (i) GCP compliance; (ii) GCP monitoring; (iii) sponsorship; (iv) IMP; (v) contents of authorization dossier; and (vi) notification of adverse event/reactions [11–15].

In the authors' view [16], as regards the first four aspects, provisions of Directive 2001/20/EC read in conjunction with Directive 2005/28/EC and with

Directive 2005/28/EC do not hinder noncommercial/academic clinical trails for the following reasons:

(1) neither Directive 2001/20 nor Directive 2005/28 oblige academic CT be in compliance with E6,CPMP/ICH/135/95 (GCP-ICH) full text and details aimed to regulatory purposes, but they require to be in compliance only with the GCP Principles (art. 1.4 Directive 2001/20) listed in Chapter 2 of Directive 2005/28 (these Principles are the same as those of ICH-GCP) and with GCP Guidelines laid down in Directive 2005/28 which are very simplified when compared with GCP-ICH. MSs are allowed by Directive 2005/28 to take into account the specificity of academic CTs as far as many issues are concerned, that is, other means instead of certain GCP details, manufacturing and import authorization, trial master file (TMF) and archiving;

(2) according to Directive 2005/28 (whereas 11) *for Academy Clinical Trial the application of certain GCP details is unnecessary or guaranteed by other means* and (art. 4) *the protocol shall provide for monitoring policy,*" academic CTs are not obliged to meet the same site monitoring and source data verification as is currently the standard in industry, their results being guaranteed in a different way;

(3) according to Directive 2001/20 (art. 2e, *Sponsor definition*) in conjunction with Directive 2005/28 (art. 7, *A sponsor may delegate any of all his functions*), each collaborating organization in academic CTs is allowed to take responsibility for its part of the CT when no person or academic organization is willing or able to take responsibility for all aspects of the sponsor role;

(4) according to Directive 2001/20 (art. 19, second sentence, *IMP shall be made available free of charge by the sponsor, unless precise condition established by MSs*), IMPs already marketed, reimbursed, and administered to patients under current medical practices do not need to be paid by academic sponsor, but can be made available free of charge for the patients, by agreement between MS National Health Services and academic sponsors;

(5) according to Directive 2001/20 (whereas 14, "*Simplified provision for IMP labeling and manufacturing in academic Clinical Trial*") in conjunction with Directive 2005/28 (art. 1.3, *MSs may introduce specific modalities for manufacturing or import authorization and the Trial Master File (TMF) and archiving in academic CT*), academic CTs are exempted from being in compliance with some specific requirements foreseen for obtaining IMP manufacturing or import authorization and foreseen for TMF and archiving;

(6) according to Directive 2001/20 (art. 9.8a) in conjunction with Directive 28 (art. 8.2), academic sponsors when using marketed drugs do not need, for the request of CT authorization, to provide Investigator' s brochure or TMF dossier that they do not have, but it is enough to refer to Summary of Product Characteristics of IMPs, already in the archives of the national RA.

Aspect of the Directive 2001/20/EC that could be modified regarding GCP and noncommercial trials.

In the authors' view, the aspects of CT Directives that should be modified to obtain the complete compliance to GCP are as follows:

- that CTs the results of which are used for regulatory purposes have to be in compliance both with ICH-GCP Principles and full text details while academic CTs have to be in compliance with GCP-ICH Principles to be either achieved by GCP-ICH details or guaranteed by other means;
- that only CTs in compliance with ICH-GCP Principles and details shall be considered for regulatory purposes while other CTs can be used only as a support, but not as a replacement, of the documentation required for the MA.

Moreover, art. 9.8 of Directive 2001/20 provides that the EC shall draw up and publish the detailed Guidance on the contents of the request for CT authorization, without taking into account the specificity of academic CTs. The EC published this detailed Guidance that has been judged as *red tape* (i.e., too prescriptive, redundant, and bureaucratic) by academic experimentalists.

In case of revision of Directive 2001/20, it might be necessary to foresee, for academic CTs, simplified Guidelines as far as it concerns CT authorization.

Finally, art. 18 of Directive 2001/20 prescribes that the EC shall draw up and publish the detailed Guidance on the collection, verification, and presentation of adverse event/reaction report, without taking into account the specificity of academic CT. The EC published this detailed Guidance; also in this case this guidance has been judged *red tape* by academic experimentalists.

In case of revision of Directive 2001/20 it might be necessary to foresee for academic CTs simplified Guidelines as far as it concerns the notification of adverse event/reactions.

1.5. GOOD CLINICAL PRACTICE AND BIOEQUIVALENCE TRIALS: GCP INSPECTIONS AND LABORATORIES

1.5.1. General Aspects

BE trials are comprised of several parts:

- a clinical part, where the test and the reference products are administered to the trial subjects and where biological samples (generally plasma or serum, possibly blood, urine, or any other suitable fluid) are collected from the subjects;
- a bioanalytical part, where the concentration of the active moiety and/or its biotransformation product(s) in the said biological samples is measured;
- the pharmacokinetic analysis, where pharmacokinetic parameters derived from these concentrations are calculated;
- the statistical comparison of the pharmacokinetic parameters obtained for the test and the reference products.

As already pointed out, EU Directive 2001/20 foresees that all CTs, BE included, have to be designed, conducted, and reported according to the GCP Principles.

For this purpose, the EMA has worked out a specific *Guideline on the Investigation of Bioequivalence*, still under evaluation at the time of writing, which replaces the previous one issued in 1998 [17].

1.5.2. EMA Guidelines on Bioequivalence Studies

The Guideline [17] sets forth requirements for the design, conduct, and evaluation of BE studies. These requirements are technical and by the same token implement the GCP Principles. A few examples on standardization and chemical analyses are given below to better illustrate these concepts.

Standardization

The test conditions should be standardized in order to minimize the variability of all factors involved except that of the products being tested. Therefore, it is recommended to standardize diet, fluid intake, and exercise.

The time of day for ingestion should be specified. As fluid intake may influence gastric passage for oral administration forms, the test and reference products should be administered with a standardized volume of fluid (at least 150 mL). All meals and fluids taken after the treatment should also be standardized in regard to composition and time of administration during the sampling period. As the bioavailability of an active moiety from a dosage form could be dependent upon gastrointestinal transit times and regional blood flows, posture and physical activity may need to be standardized.

The subjects should abstain from food and drinks, which may interact with circulatory, gastrointestinal, hepatic or renal function (e.g., alcoholic or xanthine-containing beverages or grapefruit juice) during a suitable period before and during the study.

Subjects should not take any other concomitant medication (including herbal remedies) for an appropriate interval before as well as during the study. In case concomitant medication is unavoidable and a subject is administered other drugs, for instance to treat adverse events like headache, the use must be reported (dose and time of administration) and possible effects on the study outcome must be addressed.

Chemical Analysis

The bioanalytical part of bioequivalence trials should be conducted according to the Principles of Good Laboratory Practice (GLP). However, as such studies fall outside the formal scope of GLP, the sites conducting the studies are not required to be certified as part of the GLP compliance certification scheme.

The bioanalytical methods used must be well characterized, fully validated and documented to yield reliable results that can be satisfactorily interpreted. The main objective of method validation is to demonstrate the reliability of a particular method for the quantitative determination of an analyte(s) concentration in a specific biological matrix.

The validation of a bioanalytical method should comprise two distinct phases: (1) the pre-study phase in which the compliance of the assay with the characteristics

listed above is verified and (2) the study phase itself in which the validated bioanalytical method is applied to the actual analysis of samples from the bioequivalence study in order to confirm the validity of the determinations.

Pre-study Phase

As validation involves documenting that the performance of characteristics of the method are suitable and reliable for the intended analytical application, commercial kits need to be re-validated for their use in bioequivalence studies. Similarly, demonstration of stability based on literature data only is not acceptable.

Study Phase

A calibration curve should be generated for each analyte in each analytical run and it should be used to calculate the concentration of the analyte in the unknown samples in the run. A sufficient number of separately prepared QC samples should be analyzed with processed test samples at intervals based on the total number of samples. In addition, it is necessary to validate the method of processing and handling the biological samples.

All activities should be performed according to pre-established SOPs. All relevant procedures and formulae used to validate the bioanalytical method should be submitted and discussed. Any modification of the bioanalytical method before and during analysis of study specimens may require adequate revalidation; all modifications should be reported and the scope/validation justified.

1.5.3. EMA Reflection Paper for Applicants Who Want to Submit Bioequivalence Performed Outside the European Union

The necessity of assuring technical and quality requirements in BE (and other) CTs, has induced the GCP inspectors WG of EMA to adopt a specific *Reflection Paper* [18] to warn the applicants who want to submit BE conducted in countries where the GCP Principles are not mandatory. The document is addressed to sponsors, CROs, and applicants, specifically in the field of generics, because

(a) the responsibility for the quality and safety of clinical trial data lies with the applicant, sponsors, and CROs;
(b) it is the applicant who is ultimately responsible for the quality of the Marketing Authorization Application (MAA) dossier;
(c) the aim of the document is to increase awareness with the responsible parties that the data submitted in a MAA should be of high quality, address safety issues, be verifiable and give guidance to the applicant on how to obtain more confidence on the trial data.

According to the guidance, for evaluation of quality the following aspects are of importance:

- *type of organization and its activities, previous inspection experience,* etc.
- *qualification of the facilities where the studies are performed;*
- *availability of audit certificates,* etc.

Further aspects that should be taken into account are

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

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

*Location and regulatory environment (EU/European Economic Area, third countries) of the clinical and laboratory sites, should be considered together with Ethics Committee and Competent Authority (*e.g.*, applicable local regulations and guidelines, national, international, trial type, specific local guidance).*

At the time of contracting a study to a CRO or developing an application dossier, the sponsor and the applicant should consider the following (as well as other) activities, which fall under their responsibility

- *quality and completeness of the protocol;*
- *validation of analytical methods;*
- *validation of clinical activities;*
- *quality system (including performance of monitoring and auditing) implemented by the CRO and the sponsor,*
- *verification of report, data listings, statistics and protocol;*
- *performance of audits by sponsor (post-study); evaluation of audit results and improvement cycles;*
- *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);*
- *audit of the clinical and bioanalytical sites;*
- *in relation to IMP production, verification of GMP certification, inspection status (and site authorization where applicable) and audit.*

A quality system approach to the sponsoring, contracting, purchase of a dossier/product, or applying for a marketing authorization 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.

1.5.4. Good Clinical Practice Bioequivalence Inspections

In a complementary way the EMA GCP Inspection WG has adopted (12 March 2008) the *Procedure for conducting GCP inspections requested by the EMEA:*

bioanalytical part, pharmacokinetic and statistical analyses of bioequivalence trials [19].

This annex describes specific items that may be verified during the GCP inspection of the bioanalytical part and of the pharmacokinetic and statistical analyses of BE trials.

According to this procedure the documents and data relating to the following topics are generally reviewed during the GCP inspection:

- *storage of the biological samples;*
- *validation of the bioanalytical method;*
- *performance of the assays;*
- *if requested, pharmacokinetic and statistical analyses of the trial data.*

Some of the major points to be taken into account during the GCP inspection reported in the document are

- *nature of the activities carried out at the laboratory;*
- *share of BE trials in this activity;*
- *command of the analytical methods used, particularly for complex methods;*
- *QA system in place at the laboratory;*
- *existence, availability, accessibility, and validity of SOPs.*

The suitability of the facilities and equipment available and their appropriateness for the activity of the laboratory and for the BE trial inspected should be checked during the inspection.

Some of the main points to be considered during the inspection regarding reference substances are

- *availability and contents of the certificates of analysis;*
- *expiry dates;*
- *storage conditions;*
- *conditions for access to reference substances.*

The key points to be considered regarding calibration and control samples are

- *dates and conditions of preparation of the stock and working solutions and of the calibration and control samples, and the number of aliquots prepared for each sample;*
- *accuracy of the calculation of nominal concentrations;*
- *conditions and duration of storage of the stock solutions, working solutions, and calibration and control samples, compared to their stability, as described in the validation report;*
- *matrix used, including the anticoagulant, if any.*

The crucial points to be considered during GCP inspections as regards the calibration for each run are

- *number of calibration samples;*
- *response function used, including weighing, if any;*
- *acceptance criteria for the calibration curve;*
- *exclusion criteria of calibration samples.*

Some of the major points to be considered as regards method validation are

- *validation protocol;*
- *completeness of the validation report, when compared to the various experiments performed.*

General aspects on sample handling at the facility may be inspected, including the following:

- *responsibilities for receipt and handling of biological samples;*
- *organization of the receipt system, including outside workdays/hours;*
- *sample registration;*
- *controls performed on receipt.*

As pointed out in this document a number of aspects should be checked for the storage of the samples collected for the inspected trial, including the following:

- *storage conditions of the trial samples;*
- *temperature records of the freezer;*
- *calibration of the thermometer and its traceability to national/international standards;*
- *alarms and other surveillance measures;*
- *consistency of the validation report with the source documents;*
- *chromatogram integrations;*
- *stability of the stock solutions and of the sample.*

The document also lists the main points to be assessed during GCP inspections regarding assays such as

- *completeness of the analytical report;*
- *assessment of the risk of sample mix-ups;*
- *assessment of the risk of sample cross-contamination;*
- *chromatogram integrations;*
- *calculation of the concentrations.*

1.5.5. Good Clinical Practice Clinical Laboratory Inspections

The EMA GCP inspectors WG has also adopted (September 5, 2007) the *Procedure for conducting GCP inspection requested by the EMEA on clinical laboratories* [20].

This procedure is merely presenting a general outline of the elements that have to be taken into account when inspecting laboratories involved in clinical trials, e.g., *analytical chemistry, clinical biochemistry, hematology, microbiology, histopathology, cytology, genetics.*

As prescribed by this document a number of key issues should be checked during a GCP inspection, namely:

- *quality system formally adopted by the laboratory (*e.g.*, GLP, GMP, ISO, EN);*
- *fulfillment of national requirements of accreditation;*
- *relevance of accreditation in the context of clinical trial(s);*
- *systems for QA and QC, including programs for internal audits;*
- *SOP system (distribution, availability, audit-trail, clinical trials, archiving,* etc.*);*
- *suitability and adequacy of premises (*e.g.*, adequate degree of separation of work areas to avoid mix-ups, contamination and interference);*
- *environmental conditions,* e.g., *temperature, airflow and air pressure, microbiological contamination*;
- *records of operation, maintenance and calibration;*
- *records of the validation for the methods used for the measuring equipment and apparatus (including computerized systems);*
- *log books;*
- *documentation of receipt (date and time), identification, condition, re-labeling, and storage of samples by an identifiable person;*
- *aliquoting and distribution for examination;*
- *handling of non-conformance, repeat analysis, and results within critical/alert ranges;*
- *material and methods according to the specification stated in the protocol/contract and/or required according to the European Pharmacopoeia;*
- *validation status of the methods, appropriately setting of limits of detection and quantification, precision/accuracy, known inferences, and specific control measures;*
- *participation in external quality programs, if applicable*;
- *systems for alerting results that are unexpected and/or significant deviations from pre-specified limits;*
- *integrity of data reported by internal QA/QC and/or sponsor's QA/QC personnel, audit certificate*.

1.5.6. Good Clinical Practice Inspections on Phase I Units

Last but not least, it is not out of place to recall that the EMA GCP Inspectors WG has also adopted (July 23, 2008) the *Procedure for conducting GCP Inspections Requested by the EMEA on Phase 1 Units* [21].

Without repeating what already stated above, some of the major points to be considered during a GCP inspection of interest to laboratories involved in Phase I studies are as follows:

QA and SOPs

- *Written procedures for every aspect of the study process (SOPs).*
- *Organization and independence of the QA group.*
- *Training on SOPs, GCP and also specific protocols.*
- *Audits on vendors and suppliers.*

Facilities

- *Security of the facility with respect to unauthorized or limited access.*
- *Back-up power supply.*
- *Storage of samples. Monitoring of the fridges and freezers.*
- *Maintenance, service, and calibration of instruments/equipment.*
- *Facilities for archiving, laboratory and pharmacy.*

Sampling

- *Documentation of processing of samples within the unit prior to shipment to the laboratory.*
- *Facilities equipped and resourced to handle the capacity of samples.*
- *Procedures for collection of urine samples.*
- *Procedures for sample management,* e.g., *collection, processing, consideration for missing and late samples, aliquoting, labeling, tracking, storage and shipment.*
- *Clocks, easily visible and synchronized.*

1.6. GOOD CLINICAL PRACTICE FOR CLINICAL TRIALS WITH ADVANCED THERAPY MEDICINAL PRODUCT

CTs with Advanced Therapy Medicinal Products (ATMPs) have to follow specific procedures and requirements and for this reason the EC Regulation (no. 1394/2007) [22] on ATMP requires that detailed guidelines on GCP specific to ATMPs be drawn up. After a public consultation on preliminary proposals to draft such a guidance [23], the draft Guideline on GCP, specific to ATMPs is about to be finalized.

This draft guideline is intended to set out GCP aspects specific to ATMPS in an area of limited experience and rapid evolution. It does not replace, but completes the principles and detailed guidelines set out in Directive 2005/28/EC and in the Note for guidance on GCP.

This specific guideline stresses that *where an ATMP contains or consists of tissues or cells, other actors than the sponsor and the investigator need to be considered: this includes tissue/blood establishments, procurement organizations, animal facilities and donors. It is important to put the role of these actors, and their applicable legislation, in the context of the roles and responsibilities for clinical trials*.

The relevant GCP Principles for ATMPs are the following:

(1) *the use of each ATMP should be traceable. The individual product should be traceable through the sourcing, manufacturing, packaging, storing, transport, delivery to the hospital/institution/private practice, administration to the subjects, reconciliation and destruction or final disposition. The system should contain sufficient detail to allow linking of each individual product to the individual subject who received the product and back to the donor, if the product or part of it originates from a donor, and vice versa;*

(2) *subjects should be followed-up during and after the completion of the clinical trial both for their own care and to allow data collection as needed. Processes should be established to enable contact with subjects to be maintained throughout the required follow-up period. The subjects should be provided with information on the treatment given and contact points (*e.g.*, subject card);*

(3) *the donation, procurement and testing of human cells and tissues used for the manufacturing of an ATMP should be carried out in accordance with the human cells/tissue and blood Directive by establishments which are qualified, accredited, designated, authorized or licensed by the relevant competent authority for the purpose of those activities;*

(4) *where tissues or cells of animal origin are used in the manufacture of an ATMP, the sourcing procurement and testing should be done in accordance with the xenogenic cell therapy medicinal products*.

The major points of this document of interest to laboratories are as follows:

- *Responsibility of the tissue/blood establishment/procurement organizations or animal facility: the tissue or blood establishment or procurement organization or animal facility should be responsible for the traceability with respect to the donation and procurement of the cell or tissue material needed for the manufacturing of the ATMP, up to the delivery of that material to the manufacturer.*
- *Responsibility of the manufacturer of the ATMP: the manufacturer is responsible for ensuring traceability during the manufacturing process up to the release of the finished ATMP to the sponsor for use in the clinical trial and its delivery to the clinical trial site, where the latter is also undertaken by the manufacturer or under their control. Where the sponsor takes care of the delivery of the ATMP from the manufacturer to the clinical trial site the sponsor is responsible for ensuring the traceability.*

1.7. GOOD CLINICAL PRACTICE AND CLINICAL TRIALS IN DEVELOPING COUNTRIES

1.7.1. The Increase of Clinical Trials in Developing Countries

Over the last few years, the number of CTs of pharmaceutical products in high-income countries and, more recently, in developing countries and low- and middle-income countries, has grown in an exponential way. According to FDA data, CTs in developing countries have grown from 9% in 2003 to 17.5% in 2007; in India, CTs have grown from 96 in 2001 to 493 in 2007 [24]. The Associated Chambers of Commerce and Industry of India (ASSOCHAM) foresees that the CTs business will grow from the present 150 million to 546 million of US dollars in 2010.

As highlighted by Dennis Normille in a paper published on *Science* in October 2008 [24], there are several reasons for the growth of CTs in developing countries:

(1) CTs that investigate the different reactions to drugs due to different ethno-genetic factors;
(2) CTs implemented in order to facilitate the setting-up of an industry or a society in a country, where the creation of new drugs market is foreseeable;
(3) the possibility to utilize a large basin of human subjects;
(4) savings higher than 50% compared to the expenses for the same research conducted in high-income countries;
(5) faster start of experimentations in developing countries, due to the less stringent legislative acts and inspections required before the authorization, as compared to Western countries. As everybody knows, the shorter the duration of the experimentation phase is, the shorter is the time necessary to introduce the drug in the market. If one considers that the drug is patented before the beginning of the trials, if a CT is performed quickly, the commercialization of a pharmaceutical product and its patent commercial exploitation has a longer duration;
(6) possibility to test drugs for diseases that characterize developing countries;
(7) possibility to conduct CTs and to recruit participants on the basis of conditions that sometimes are not easily accepted in Western countries.

Even academic researchers that promote CTs without the economic support of pharmaceutical industries, when making a decision to conduct their research in developing countries, try to take advantage of the more permissive setting.

It is clear then, that there are several different reasons that justify the choice to perform CTs in developing countries, starting from economic, organizational, operative, clinical, and ethno-genetic reasons, to other reasons related to the necessity of finding shorter and simpler ways to implement experimentations of pharmaceutical products. Such ways utilize short cuts that apparently avoid only bureaucratic obstacles, but that actually elude the strict independent ethical and scientific evaluation necessary to authorize a CT in order to guarantee human rights protection, health and well being of participants, and the objective methodological severity of

research. For the above-mentioned reasons it happens frequently that in the developing countries unethical CTs are conducted [25].

1.7.2. European Union Legislation and Clinical Trials in Developing Countries

The described and progressive increase in the number of CTs conducted in developing countries is determining an increase in the request for authorization of marketing for drugs based on efficacy data from CTs conducted in developing countries. The acceptability and reliability of those data depends, in line with the European normative [26], on two factors:

(1) that the CTs are conducted according to the ethical Principles of GCP
(2) that the CTs are conducted according to the scientific and procedural Principles of GCP.

The EU has no direct control over regulation of CTS carried out in third countries. The EU Regulation 726/2004 [27] lays down the procedures for the supervision and the authorization by EMA of medicinal products for human and veterinary use. In the opening, the Regulation calls upon the need to ensure the ethical requirements of Directive 2001/20/EC: *In particular, with respect to CTs conducted outside the Community on medicinal products to be authorized within the Community, at the time of the evaluation of the application for authorization, it should be verified that these trials were conducted in accordance with the Principles of GCP and the ethical requirements equivalent to the provisions of the said Directive*.

However, a recent report by the Wemos Foundation [28] shows that most European registration authorities do very little to ascertain whether CTs of drugs conducted in developing countries for subsequent MA in the EU are actually conducted in an ethical manner. Of the 25 EU registration authorities to which Wemos submitted a questionnaire based on the Declaration of Helsinki, only 12 responded, representing both the old and the new EU MSs. As a result, drugs that have not been tested according to ethical standards are entering the EU market [29].

For the evaluation of drugs for human use that are only for export (such as malaria) or for CTs applications done outside the EU, Regulation 726/2004, in article 58, envisages the possibility of issuing a scientific opinion by the EMA. This provision was included by request of the WHO to prevent a reduction of R&D of new drugs (especially vaccines) as well as a reduction in their supply to developing countries. Current legislation, in fact, does not obligate US, European and RAs of other countries to review CTs applications done outside their countries or to check whether the products are only for export.

As a consequence, these authorities rarely perform GCP trial inspections in developing countries, except in case the results are to be submitted to a centralized EU MA. At the same time, developing countries RAs, where in place, are called to be primarily responsible for licensing of priority drugs in their countries, when, in the past, they used to rely on the regulatory evaluation of the agency in the country of origin.

For the above-mentioned reasons, EMA in its strategy paper [30] on this topic, states that it will give greater priority to ethics when granting MA to medicines that have been tested outside Europe. In this framework EMA has recently established the *EMEA Working Group on third country CTs*, with the aim to develop practical proposals for tasks and procedures, or guidance, in the action areas identified in the EMA strategy paper *Acceptance of CTs conducted in third countries for evaluation in Marketing Authorization Applications*.

In this context, one of the objectives of the WG is drafting a Reflection Paper to provide guidance on how to cooperate in the regulation of CTs in developing countries and to contribute to capacity building through the existing initiative or by implementing new ones.

The *EMEA WG on third country CTs* should set up priorities and prepare an action plan on how to push forward this topic. However, for doing that, it is important to know what are the different initiatives implemented by the various organizations and institutions at the national, regional, European, and international level in order to avoid duplications and to contribute to capacity building in a more efficient way.

As pointed out by the Italian Medicines Agency (AIFA) in the conclusive document of the International Round Table AIFA-UNICRI on *Biomedical Research in Developing Countries* held in Rome on December 2008 [31], the final aim of the collaboration in the field between Developed and Developing Countries should be to ensure that in Developing Countries at least the following instruments are in place:

(1) legal provisions that require the GCP compliance for CTs and that permit trials on drugs to be performed only if duly authorized, all violations being sanctioned;
(2) the actual existence of Research Ethics Committees truly independent and professionally sound;
(3) systems of control (GCP Inspectorates) of CTs before, after, and during their performance;
(4) legal provisions that allow drugs to be marketed only if duly authorized, all violations being sanctioned;
(5) legal provisions that envisage the possibility of refusal by RAs to authorize marketing of drugs for which safety and efficacy has been shown through trials which are not conducted according to the GCP ethical, quality, and scientific principles.

It is firmly held that the achievement and the implementation of the above-mentioned requirements not only in developed countries but also in developing countries where CTs are performed, can allow the GCP Principles to be complied with. This goal can be obtained only by a coordinated, harmonized, and integrated collaboration between developed and developing countries for the capacity building of the legislative and operative framework necessary for a worldwide implementation of the Principles of GCP.

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