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Review Article

GCP inspections in Germany and Europe following the implementation of the Directive 2001/20/EC

GCP-Inspektionen in Deutschland und Europa nach Implementierung der Direktive 2001/20/EG

Abstract

Background: The implementation of the Clinical Trials Directive 2001/20/EC and the Good Clinical Practice Directive 2005/28/EC fundamentally restructured and harmonized the conduct of clinical trials in Europe. GCP inspections – which affect study sites, laboratories, sponsors and contract research organizations (CRO) alike – make up an important part of these regulations. A common understanding of how these regulations apply in daily life is however not always ensured.
Methods: A working group of the Clinical Research/Quality Assurance subcommittee of the German Association of Research-Based Pharmaceutical Companies (VFA) was established to outline the regulatory requirements, the experience gathered with inspections by means of a survey and to set up guidance on how to manage an inspection.
Results and conclusions: The survey, conducted with the help of 15 pharmaceutical companies within the VFA, included a total of 224 inspections (74 inspections in Germany, 150 from other European countries). Most frequent findings in and outside Germany were related to "documentation" (40.5% vs. 21.3%), "investigational new drugs" (16.2% vs. 14.7%), "drug safety" (13.5% vs. 8%) and "application for a clinical trial authorization" (5.4% vs. 12%).
From a German perspective, key findings of this working group were the necessity for a clear differentiation of responsibilities between national and federal as well as international authorities, a harmonization of inspection procedures and topics, and a clarification of whether pre-study/on-study and pre-approval/post-approval GCP inspections of the federal higher authority are included in the "Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten" (ZLG) requirements. The survey illustrated, that inspections usually are conducted at the investigational site, and that most of the findings are well known and thus could be prevented by communicating and discussing audit results more intensely within study groups. Again, the survey illustrated, that a harmonization of inspections appears warranted. Finally a code of practice is provided that considers these findings and delivers a basis for a successful inspection whether at the sponsor or the GCP site.

Keywords: GCP inspection, Implementation Directive 2001/20/EC, frequency, survey, sponsor inspection, code of practice

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Zusammenfassung

Hintergrund: Mit Implementierung der „Clinical Trials" Direktive 2001/20/EG sowie der „Good Clinical Practice" Direktive 2005/28/EG wurde die Durchführung von klinischen Prüfungen in Europa umfassend neu geregelt und harmonisiert. GCP-Inspektionen sind ein wesentlicher Bestandteil dieser Regelungen und betreffen Prüfstellen, Labore, Sponsoren und Auftragsinstitute (contract research organizations, CROs) gleichermaßen. Häufig fehlt es jedoch an einem allgemeinen Verständnis

darüber, wie diese Regelungen in der täglichen Routine anzuwenden sind.

Methoden: Eine Arbeitsgruppe des Unterausschusses Klinische Forschung/Qualitätssicherung des VFA (Verband Forschender Arzneimittelhersteller) erstellte eine Übersicht der regulatorischen Anforderungen zu GCP-Inspektionen, erfasste Erfahrungen mit Inspektionen mittels einer Umfrage und erarbeitete einen Leitfaden zur Begleitung einer GCP-Sponsor-Inspektion.

Ergebnisse und Schlussfolgerung: Die Umfrage, die mit Unterstützung von 15 im VFA organisierten pharmazeutischen Unternehmen durchgeführt wurde, umfasste eine Gesamtzahl von 224 Inspektionen (74 Inspektionen in Deutschland, 150 aus anderen europäischen Ländern). Die häufigsten Befunde innerhalb und außerhalb Deutschlands bezogen sich auf die „Dokumentation“ (40,5% vs. 21,3%), „Prüfmedikation“ (16,2% vs. 14,7%), „Arzneimittelsicherheit“ (13,5% vs. 8%) und den „Antrag auf Genehmigung der klinischen Prüfung“ (5,4% vs. 12%).
Aus deutscher Sicht sind die wichtigsten Erkenntnisse der Arbeitsgruppe die Notwendigkeit einer klaren Abgrenzung der Verantwortlichkeiten zwischen lokalen, nationalen und internationalen Behörden, eine Harmonisierung der Inspektionsdurchführung und -inhalte, sowie eine Klärung ob die ‚pre-study/on-study’ und ‚pre-approval/post-approval’ GCP-Inspektionen der Oberbehörden den von der „Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten” (ZLG) vorgelegten Anforderungen entsprechen. Die Umfrage ergab, dass Inspektionen routinemäßig an Prüfstellen durchgeführt werden; die meisten Inspektionsbefunde sind bekannt und könnten durch eine verbesserte Kommunikation und Diskussion der Befunde mit den Studiengruppen vermieden werden. Die Umfrage bestätigte auch, dass eine Harmonisierung der Inspektionen notwendig erscheint. Abschließend wird ein Leitfaden unter Berücksichtigung der Umfrageergebnisse vorgestellt, der als Basis für die erfolgreiche Begleitung einer Behörden-Sponsor- oder Prüfstellen-Inspektion verwendet werden kann.

Schlüsselwörter: GCP-Inspektion, Implementierung der Direktive 2001/20/EG, Häufigkeit, Umfrage, Sponsor-Inspektion, Leitfaden

Introduction

The ICH directive E6 defines “Good Clinical Practice“ as “*a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the right, integrity, and confidentiality of trial subjects are protected*” (ICH E6, glossary 1.24 [1]). The efficiency of these measures is ensured by internal audits by the sponsor (ICH E6, glossary 1.6 [1]) and external inspections by the authorities (ICH E6, glossary 1.29 [1]).
In the course of the Clinical Trials Directive 2001/20/EC implementation by the 12th amendment to the German Medicines Law (*Deutsches Arzneimittelgesetz*) and the GCP regulation in 2004 external inspections by the higher authorities were fundamentally revised. Since the interpretation of these regulations is subject to continuous refinement, it is essential for research-based pharmaceutical companies to be sure about the expectations of authorities and to be aware of the specific conduct of these GCP inspections.

Therefore a working group of the Clinical Research/Quality Assurance subcommittee of the German Association of Research-Based Pharmaceutical Companies (Verband *Forschender Arzneimittelhersteller*, VFA) was established to

1. compile an overview about existing guidelines, laws and regulations
2. compile the hitherto experience with GCP sponsor inspections after implementation of the Clinical Trials Directive 2001/20/EC
3. develop a code of practice for expert assistance during GCP sponsor inspections.

Overview about existing guidelines, laws and regulations

The European Medicines Evaluation Agency (EMEA) was founded in 1993 based on the order 2309/93/EC to provide a centralized European licensing and supervision procedure for pharmaceutical drugs. Article 51 of this order specifies “that co-ordinating the verification of

compliance with the principles of (...) good clinical practice" is one important task of the EMEA.
To comply with this order a *GCP Inspection Services* Group was founded in 1997 by the EMEA to advise and support the community, the commissions, the member states and the EMEA in issues regarding GCP and inspections. The working group consists of GCP inspectors from member states and the chairman is recruited from within the EMEA-section for inspections. As of July 2007 this group was renamed into *GCP Inspectors Working Group* (GCP IWG) and a detailed description of the mandate, the aims and regulations of this working group was provided [2].
Attachment 1 gives an overview about the European directives and international rules considering GCP inspections. It took more than 10 years and several revisions of the respective orders until specific requirements for inspectors and descriptions of the procedures were published within the guidance 2005/28/EC in 2005. In chapter IV of the EUDRALEX Volume 10, published in 2006, prerequisites for GCP inspectors and the conduct of GCP inspections were laid down in detail. The GCP IWG published a description of how to coordinate, prepare, conduct and report GCP inspections within the centralized licensing procedure on the EMEA homepage in May 2008 [3]. The description contains detailed information on the content and extent of inspections at the investigational sites, laboratories, sponsor's site, clinical research organizations (CROs), phase-I-units, as well as computer systems, file structure and archiving.
The implementation of the European legislation into national German law is displayed in Attachment 2. In preparing this table the respective paragraphs of the German Medicines Law (*Arzneimittelgesetz*, AMG) and the GCP order (*GCP-Verordnung*, GCP-V) were combined. The situation in Germany is special in that there is a task sharing between the federal higher authority and local authorities within federal states. The federal higher authority is responsible for approving clinical trials and licensing pharmaceuticals. The federal state authorities are responsible for routine or cause specific supervisions of sponsors, investigational sites or other institutions and are confederated since 1994 (*Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten*, ZLG).
A description of the different types of inspections in Germany can be found in the General Administrative Fiat for Conducting the Medicines Law (Allgemeine *Verwaltungsvorschrift zur Durchführung des Arzneimittelgesetzes*, AMGVwV) [4]. Detailed and publicly accessible procedural instructions regarding inspections of clinical trials of pharmaceutical drugs which are subject to authorization have been published by the ZLG on their website in 2007/2008 [5].
Attachment 3 contains further helpful and publicly accessible information sources regarding GCP inspections. Highly recommended is the EMEA website containing among other Standard Operating Procedures (SOP) for GCP inspection issues [6]. Of particular interest for sponsors based in Germany is the ZLG website [7], which provides a detailed and excellently rehashed overview of national and international regulations as well as links to international and national authorities.
Taken together and in reviewing the available information the following issues are desirable from the sponsor's side:

1. a clear differentiation of responsibilities between national and federal as well as international authorities,
2. a harmonization of inspection procedures and topics are warranted when comparing different federal state authorities, in particular for Germany. An identical interpretation of GCP laws and guidelines is mandatory. A first step into this direction has been undertaken by formation of the ZLG and their publicly available procedural requirements. A guideline on how to interpret these procedural requirements is however essential.
3. It remains unclear whether these procedural requirements also include pre-study/on-study and pre-approval/post-approval GCP inspections of the federal higher authority.

Ideally a continuous dialogue between authorities and sponsors regarding the correct interpretation of the regulatory basis of GCP and the resulting steps for improving quality should be established aiming at improving clinical research and patient safety in Germany.

Experience with GCP sponsor inspections – results of a survey in Germany and Europe

Publicly available reports of GCP inspections are rare [8], [9], [10] and mostly from Great Britain. Therefore a survey was conducted between January 2005 and June 2007 among 45 pharmaceutical companies organized within the VFA (German Association of Research-Based Pharmaceutical Companies) to determine the frequency, type, reason and the reported findings of GCP and pharmacovigilance inspections after the directive 2001/20/EC at investigational and sponsor sites in Germany and Europe (for detailed information see [11]). Despite two reminders, only 15 companies – most of them member of the Clinical Research/Quality Assurance subcommittee – provided an evaluable questionnaire. This reflects a response rate of 33.3% within the VFA, who represents more than 2/3 of the German pharmaceutical market and research activities. The companies reported a total of 224 inspections (74 inspections in Germany, 150 from other European countries). This corresponds to an inspection rate of about 50 per year (GCP site inspections > sponsor inspections). Of note, the survey only included clinical trials performed by the pharmaceutical industry and does not reflect the situation of investigator initiated research, which might be different.
The questionnaire asked for information about all GCP sponsor, GCP site and pharmacovigilance inspections within Europe starting 2005. Specifically we asked for the type of inspection, the responsible inspecting authority

(e.g. Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), Paul-Ehrlich-Institut (PEI), Medicines and Healthcare products Regulatory Agency (MHRA), local authority), the reason for the inspection (e.g. Pre-Clinical Trial Application, pre-approval, for cause, routine) and for the findings of the inspection.

The frequency of sponsor inspections and inspections at the investigational site differs substantially when comparing Germany to the rest of Europe (Figure 1). Remarkable was, that no combined inspections were conducted in Germany, while this was the case for 12% of inspections in Europe. Investigational site inspections were most frequent both in Germany and Europe. Pharmacovigilance inspections have a low share (10% of total) of the total inspections (8/74 in Germany; 15/150 in Europe).

From 73 out of 224 reported inspections a total of 184 findings were reported. The range of findings is displayed in Figure 2. Most frequent findings in and outside Germany were related to "documentation" (40.5% vs. 21.3%), "investigational new drugs" (16.2% vs. 14.7%), "drug safety" (13.5% vs. 8%) and "application for a clinical trial authorization" (5.4% vs. 12%).

Results classified as related to "*documentation*" include instructions for preparing the Case Report Form (e.g. naming the total number of pages, verification of every single in- and exclusion criterion, frequency of investigator signatures), the completeness of physician's documentation (GCP compliant corrections of the CRF, locating the patients' informed consent and emergency envelopes, completeness of medical history within the patient's documentation), missing documents (e.g. investigators brochure, monitoring report), disposition of source documents (quality of life questionnaires), and CRF copies at the investigational site, traceability of trial approval (mostly in case of amendments).

Results classified as related to "*investigational new drugs*" include the necessity of labeling in case of prolonged storage life of medication, uniformity of the labeling text in case of multi-lingual labels, access to and storage of investigational drugs, clarity of medication tracking and improvements of temperature control (if necessary).

Results related to "*drug safety*" were adherence to deadlines and their documentation in case of severe adverse events and suspicion of unexpected serious adverse events as well as the reporting of non-serious events and their documentation.

Results related to "*application for a clinical trial authorization*" include non-appropriate use of the investigator definition, the late submission of amendments, poor patient information and missing recent certificates of insurance at ethics committees and authorities but also the missing documentation of ethics committee composition.

Findings from pharmacovigilance inspections (3/8 inspections in Germany and 7/15 in Europe) were: improved compliance with reporting deadlines, faster contact to the authorities in case of newly recognized safety concerns, an improved training for contract partners, the continuous reachability for questions relating to drug safety and improved database applications. In addition to these the availability and content of standard operating procedures (SOP) was a further finding in other European countries.

Taken together these are the most important survey results:

1. GCP site inspections were much more frequent than sponsor inspections
2. In Germany inspections are (as opposed to other European countries) conducted by a variety of authorities. Of note, recently the number of local authorities in North Rhine-Westphalia was reduced from 59 to 1 central authority for this Federal State.
3. Most findings from these inspections are well known and could be addressed to the sites in order to avoid them in the future.
4. The German Drug Law uses an inconclusive definition of the "investigator", leading to the obscure situation that every physician involved may be regarded to be an "investigator", resulting in everyday practice in some under- and/or overreporting to concerned authorities and Ethics Committees.

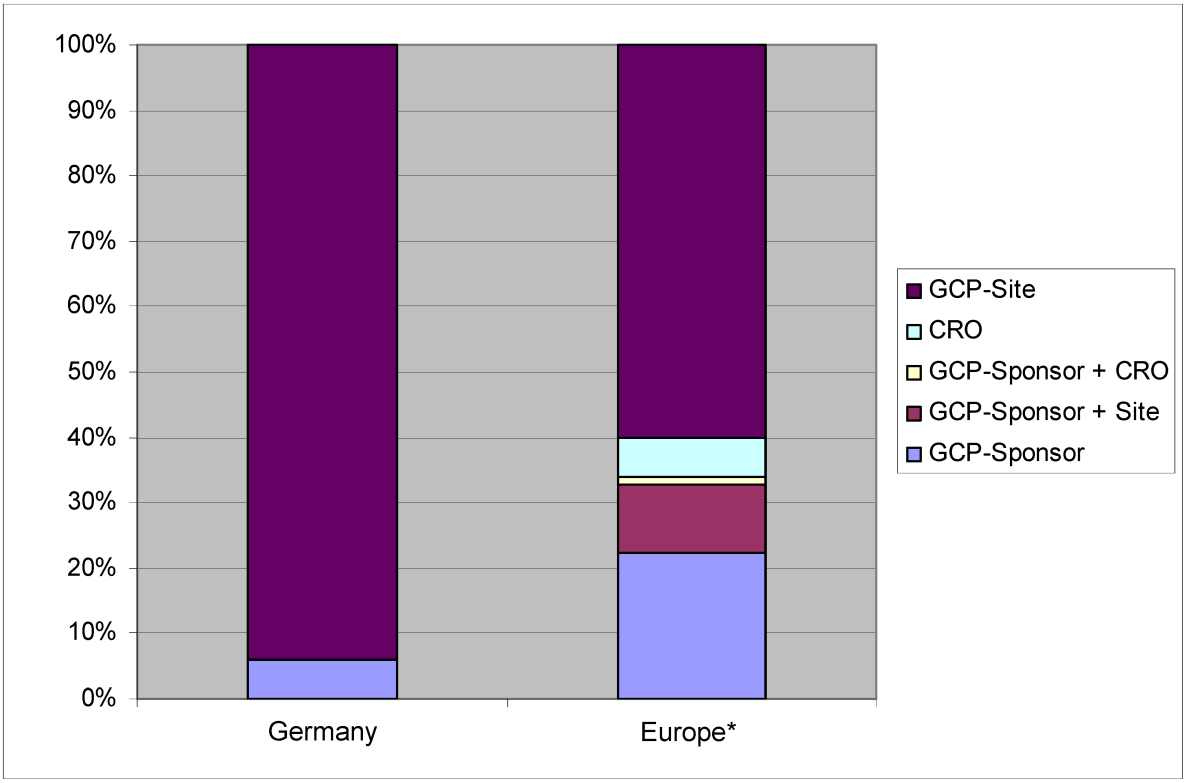
Code of practice for expert assistance during GCP sponsor inspections

Table 1 displays the items of a GCP sponsor inspection which were derived from a recent international GCP sponsor inspection and from further sources like the ZLG procedural requirements "Procedures for inspections in clinical trials subject to authorization on pharmaceutical drugs". The ability to generalize is however restricted due to different internal organizations and thus the code of practice has to be adapted to prepare for an inspection. The following steps are necessary for the preparation, conduct and follow-up of an inspection.

Preparation

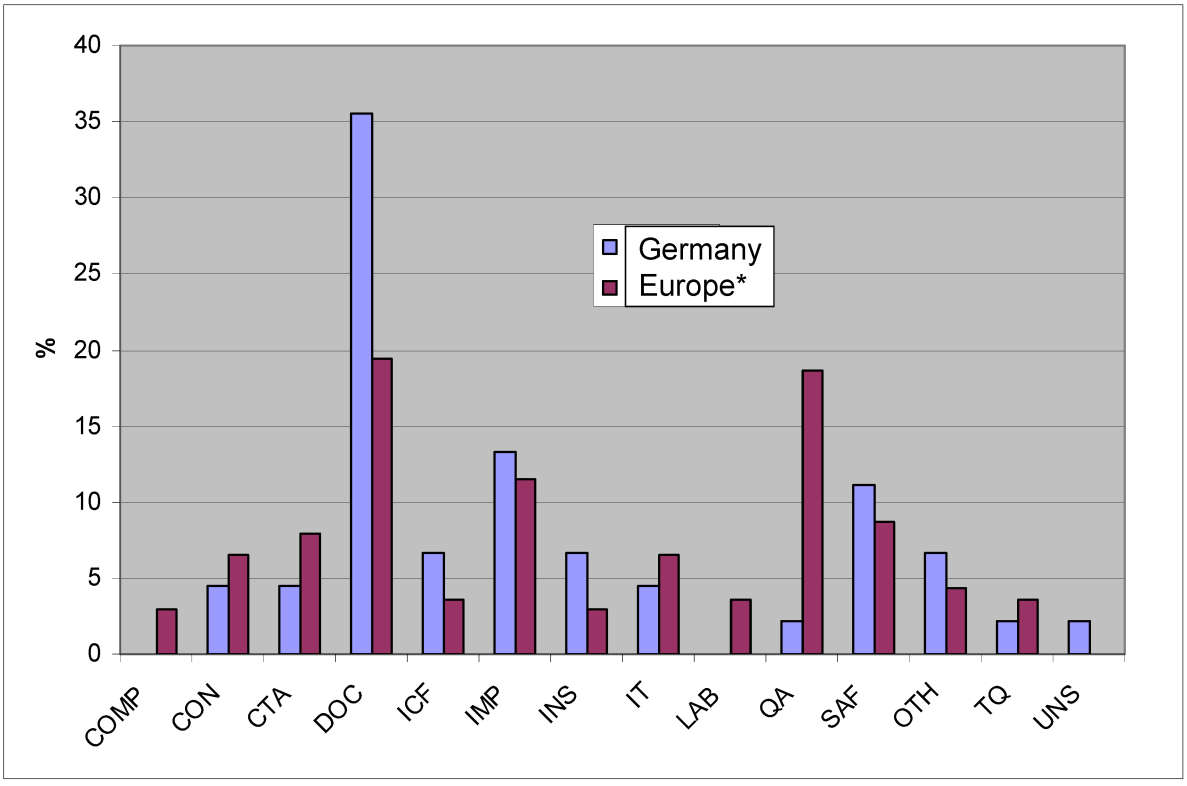
In the course of the written notification of a GCP inspection a number of information regarding the company are requested. These include organizational charts, overviews of ongoing or completed studies within a particular time frame and lists of standard operating procedures. A draft agenda may be provided.

Additional documents that may be requested before the inspection include: completed questionnaire, list of SOPs as well as provision of selected SOPs, list of used and validated computer systems (including validation documents for a particular system), description of archives used, contract templates, certificate of insurance. While the inspection date is usually not negotiable, the agenda may have room for discrete changes.



* (without Germany)

Figure 1: Type of inspections in Germany in comparison to Europe (without Germany) [11]



COMP = Compliance, CON = Contracts, CTA = Clinical Trial Application, DOC = Documentation, ICF = Informed Consent Form, IMP = Investigational Medicinal Product, INS = Insurance, IT = Information Technology, LAB = Laboratory, QA = Quality Assurance, SAF = Safety, OTH = Other, TQ = Training & Qualification, UNS = undetermined, * (without Germany)

Figure 2: Findings from site inspections (from a survey of VFA companies in Germany [11])

Table 1: Scope and content of a GCP sponsor inspection

Topics	Comments
Inspectorate/authority	Name, authority
Type of inspection	e.g. Pre-Clinical Trial Application, Pre-approval

Scope of inspections	
Organisational structure	Illustration of inspected clinical trial sites, integration and crosslink with other local units, e.g. approval and drugs safety, integration into international structures such as global drug safety, clinical quality assurance
Project-/Study management	Tasks and organization of the project- or study management including the proxy, handling of fraud
Monitoring	Tasks and organization of the monitoring function
Data Management & Statistics/Biometry	Tasks and organization of biometry and data management
Pharmacovigilance	Tasks and organization of drug safety, overview of procedures for registration, reporting of undesirable events, evaluation within the local or global drug safety, reports of SUSARs (suspected unexpected serious adverse reaction) and annual safety reports for authorities, ethical committees and investigators, cooperation between site and drug safety, permanent possibility of code breaking
Regulatory affairs	Tasks and organization of regulatory affairs, in particular differentiation of national and international functions, notification of trials
Clinical Quality Assurance/Quality Assurance (QA)	Tasks and organization of quality assurance units, audit masterplan, templates for audit reports and corrective action plans, no general access to auditing reports
Medical responsibilities	Involvement of departments beyond clinical research into decisions and consulting, e.g. responsible clinical expert, medical surveillance of trials, replacement provisions, support of compassionate use programs, non-interventional studies, investigator sponsored studies
Medical writing	Tasks and organization of the "medical writing", preparation of the study protocol and report of studies including the used IT infrastructure (document management system)
Investigational drugs	Illustration of the distribution of investigational drugs from manufacturing and release, distribution to the sites as well as redemption and destruction, documentation and labelling, manufacturing approval, procedures for re-labelling, import approval from non-EU countries, procedures for recall, responsibility/timeline for the preservation of retained samples

(Continued)

Table 1: Scope and content of a GCP sponsor inspection

Scope of inspections	
Legal	Use of standardized templates, integration of the legal department, contract with investigators, licensing partners and use of standardized procedures, involvement of the legal department, contracts with investigators, licensing partners and service providers
Patients insurance	Regulation of insurance obligations of clinical studies, responsibilities
SOPs and document control	Illustration of SOP systems (e.g. web based), responsibilities for the preparation, continuous verification and update
Training, Qualification	Documentation of training facilities, e.g. group training, web based training, hands on training such as monitoring visits, illustration of training, e.g. training documents, databases, routine update of curricula vitae
Archive	Description of different archiving hierarchies, e.g. current study documents at the office, intermediate archive within the office building, final internal archive, external archive. Description of the procedure of archiving, the timelines for preservation and regulations for access to the archive
Laboratories, other external partners	Accreditation, qualification of external laboratories and partners
Information systems	Illustration of study databases, study management software including data protection
Computer Systems Validation (CSV)	System overview of different requirements for validation. Preparation of a list of all GCP relevant systems with responsibilities and the location of the respective documentation. Criteria for GCP relevance (patient safety, data quality, product quality). Inspection of the documentation of validation for selected systems or an internal release document.

Study specific preparation	
Trial Master File	Explanation of the Trial Master File SOP, introduction of electronic Trial Master Files, verification of TMFs of selected studies, archiving at the investigator

The internal preparation for the inspection include the following: short presentation to introduce the company (20 min), recent organizational charts, identification of staff for interviews and training for the participants (usually staff that conducts the trial), up to date curriculum vitae, recent SOP (ensuring that staff is familiar with these), expert translator if necessary, logistical organization (meeting room, copy machine, telephone, fax and IT infrastructure).

Conduct (example)

At the first day of the inspection frequently there is a common meeting with inspectors and staff of the sponsor. During the course of this meeting the inspectors illustrate the reason for the inspection (legal requirements). The company then has room for a short introduction before the final agenda is agreed upon and logistic questions answered. At the workplace of the inspector(s) the following material has to be provided: organizational charts for all departments subject to inspection, the most relevant clinical and pharmacovigilance SOP, curriculum vitae, job descriptions, training documentation for interview partners, trial master file, contracts, case report forms and others. These and all documents that are requested during inspection should be labelled to be confidential and every single item recorded. The inspectors will read through the documents provided and conduct a considerable number of interviews. It is also important to record the questions during the interview (usually task of Quality Assurance). Documents requested by the inspectors have to be delivered as soon as possible.

The active phase of the GCP inspection ends with a discussion, at which the inspectors summarize and assess the essential results and the company has the opportunity to explain these. Again a detailed protocol is mandatory.

Follow-up

Inspections require as much time for follow-up as for preparation. The information constitute an independent feedback which is highly welcome to improve the internal organization. The following steps are very important: forward pending documents to the inspectors, analyze the orally presented results, prepare the comments to the authority and the workup, in case of serious findings initiate the appropriate measures, prepare investigational sites for a subsequent inspection, and answer to the inspection report and the actions derived from that. Most authorities grade the results as “minor”, “major” or “critical”. Further findings can be categorized into “Non-compliances”, “Recommendations” and “Observations”.

Conclusions

The implementation of the "Clinical Trials" Directive 2001/20/EC and the "Good Clinical Practice" Directive 2005/28/EC fundamentally restructured and harmonized the conduct of clinical trials in Europe. GCP inspections – which affect study sites, laboratories, sponsors and contract research organizations (CROs) alike – make up an important part of the regulations laid down in these directives.

The publication of the procedures for conducting GCP inspections by the EMEA GCP Inspectors Working Group and the publication of procedures for inspections of clinical trials of medicinal products by the German Central Authority of the federal states for Health Protection with Regard to Medicinal Products and Medical Devices have helped increase transparency and harmonization [5].

There is however room for a differential interpretation of these guidelines and guidance on how to apply these is warranted. This is particularly important in countries like Germany in which many different authorities interact and perform GCP inspections. A close dialogue between the competent authorities and the sponsor about the interpretation of fundamental regulatory requirements with regard to GCP would improve the quality of clinical research and reduce the uncertainties when being inspected by different authorities.

The survey on GCP inspections at the sponsor’s site organized within the VFA on the other hand showed a rather consistent picture of inspection frequency, site of conduct and important findings. It is the more surprising that key learnings from these inspections are obviously not used to improve the results of subsequent inspections; results of repeated inspections are frequently quite similar. A more intense follow-up and interchange between companies should allow to raise the awareness for the most salient points and thus increase the quality of clinical trial conduct. The provided guidance may represent an essential step into this direction.

Taken together Germany, after the "Clinical Trials" Directive 2001/20/EC, has further strengthened its position as a competitive location for clinical research. This can be demonstrated by the increasing number of clinical studies in Germany and the excellent quality of its investigational sites.

Notes

Conflicts of interest

None declared

Attachments

Available from
http://www.egms.de/en/gms/2009-7/000060.shtml

1. GMS-Goebel-Attachment1.pdf (39,47 KB)
   Attachment 1: International orders and guidelines with respect to GCP inspections
2. GMS-Goebel-Attachment2.pdf (31,21 KB)
   Attachment 2: National (German) orders, guidelines and laws with respect to GCP inspections

3. GMS-Goebel-Attachment3.pdf (45,49 KB)
Attachment 3: Further useful sources of information on GCP inspections

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