First inspection of a Legal Representative in the EU by local authority

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1. The Mechanisms of Legal Representation in the European Community

2. What it probably should be and what it might look like

3. First inspection of a Legal Representative in the EU by local authority
What is it and what is it not?

- Is the legal representative of the sponsor:
  - The agent or lawyer of the sponsor?
  - The supervisor of the sponsor?
  - A small edition of the sponsor?
  - A one to one copy of the sponsor?

- There is no uniform opinion in all EU member states.
- The inspecting authority in the member state where the legal representative is established will have an idea.
- You will only know when it comes to a lawsuit – or if a guideline is issued.
The implementation of the EU Clinical Trials Directive 2001/20/EC on 1 May 2004 harmonized clinical drug studies in EU member states concerning:

- Implementation of ICH-GCP and EU guidelines
- Protection of study subjects
- Manufacture of study medication
- Approval procedures
- Studies with minors, incapacitated adults
- Safety reporting
- Inspections
The legal representative

- Directive 2001/20/EC, Article 19
  - This Directive is without prejudice to the civil and criminal liability of the sponsor or the investigator. To this end, the sponsor or a legal representative of the sponsor must be established in the Community.

- You will not find more provisions in the legal texts implementing this directive into national law.

- Actually, you will find less than that!
Some additional guidelines (1)

- **Vol. 10 - Notice To Applicants – Qs/As, Question 3 a:**
  - If the sponsor is not established in the EU, a legal representative of the sponsor must be established in the EU.
  - The legal representative shall have the position of the sponsor with regard to civil and criminal liability in the EU.
  - It is acceptable to use an established company as a legal representative.
  - Only one legal representative can act on behalf of one sponsor in one clinical trial.
• **Vol. 10 - Notice To Applicants – Qs/As, Question 3 a:**
  
  • It is not acceptable to divorce responsibilities of liability for trial conduct.

  • If the sponsor conducts several different trials in the EU, the legal representative does not have to be the same for all trials – but it is acceptable to have one (central) legal representative for all trials.

  • The applicants for the application to the competent authority and the Ethics Committee might be different from the legal representative.
What do you need it for?

- For all clinical drug studies in the EU:
  - If a sponsor of a clinical study is established outside the European community and wants to perform a study in an EU member state, a legal representative is required which is located in the EU.
    - Evidence has to be provided in the application dossier.
    - Evidence has to be provided if access to the electronic database for safety reporting (EudraVigilance) is established.
When else do you need one?

- Application for authorisation of drugs or biologicals
  - Directive 2001/83/EC requires that for a marketing authorization application the applicant has to be established in the EU.

- Application for an orphan drug designation
  - Regulation (EC) No 141/2000 requires that the sponsor seeking to obtain or having obtained the designation of a medicinal product as an orphan medicinal product must be established in the EU.
Consequences

- The legal representative of the sponsor has to take care of two issues:
  - Legal requirements:
    - Insurance(s) against liability has (have) to be provided.
  - Requirements of Good Clinical Practice:
    - The clinical trial has to be supervised to ensure it is compliant to ICH-GCP, putting the legal representative of the sponsor in the position of the acting sponsor.
• With all this in mind, FGK-RS was founded as a company separate from FGK Clinical Research GmbH (FGK-CR).

• If there will ever be a problem with liability issues of studies supervised by FGK-RS, FGK-CR will not be affected.

• FGK-RS can provide the service of legal representation of the sponsor as a stand alone service, without FGK-RS or FGK-CR being the CRO which conducts the study.
How FGK-RS was set up: SOPs

- SOP „Assessment“
  - Risk assessment of clinical studies and marketing authorization applications for which FGK was asked to act as a legal representative of the sponsor / applicant.

- SOP „Activities during Clinical Studies“
  - Describes major operations necessary to perform duties and functions which are transferred to FGK.

- SOP „End of Study / Archiving of Study Documentation“
  - Describes the transfer of study documents to the sponsor and the process for archiving of study related documents after a clinical study has been completed.
History of the inspection

- 21 February 2008: E-mail and call from Bavarian authorities (BA): Announcement of an inspection, request for overview of current studies in Germany
- 27 February 2008: E-mail to the BA with the requested study overview
- 7 March 2008: E-mail from the BA: Specification of one study and provision of the agenda for the inspection
- 12 March 2008, 10:15-19:15h and 13 March, 9:00-15:00 h: Conduct of the inspection
- 6 June 2008: Inspection report from BA received
- 10 July 2008: Reply sent to BA
Focus of the inspection

- Presentation of FGK Representative Service GmbH
- Review of sponsor tasks for a specific study:
  - Quality assurance system, audit system
  - Staff
  - Pharmacovigilance
  - Assignment of responsibilities, contracts
  - Communication with authorities, ethics committees
  - Study medication
  - Documentation, archiving of records
  - Responsibility for monitoring
  - Selection of study centers
What the inspectors found

- Critical deficiencies: None
- Serious (major) deficiencies: None
- Comments: 16
Comments: People

1. It is unclear how suitably qualified personnel is available to ensure that the tasks and obligations of a sponsor's legal representative can be met (especially, persons with specialist medical knowledge).

2. Some job descriptions are undated and some do not include GCP-specific activities.

3. There should be a system for documentation of regular training, definition of training needs, training plan, evaluation of training success.

4. It is not clearly stipulated which clinical trial tasks are assumed by FGK-RS, which activities are delegated.
5. The procedure for retrieving emails is not conclusively set forth in an SOP.

6. There should be rules for parallel filing of pdf and Word files, for storage of all study documents in electronic form, for review of completeness of records, for a consistent folder structure.

7. Access the FGK-RS servers should be limited to FGK-RS employees.
8. The contract does not provide that FGK-RS is informed about the study status (enrollment of first patient, major deviations, SUSAR reporting, access to all study documentation).

9. FGK-RS has no knowledge on compliance at the investigating sites and of the number of study subjects.

10. FGK-RS has no information if the CRO forwarded two SUSAR reports to the investigating sites.

11. FGK-RS has no knowledge of current monitoring status, covering at least summary reports outlining monitoring status and major deviations.
12. A quality assurance system for FGK-RS has to be improved to cover, e.g., particulars on archiving, major documents (ethics committee opinions, authorizations by the health authorities, insurance policies, pharmacovigilance data), policy on access to pharmacovigilance data.

13. A quality assurance unit is not set up at FGK-RS.

14. There are no rules on permission of printing SOPs and on informing employees about changes in SOPs.

15. No self-inspection has been conducted at FGK-RS.
16. To ensure the requisite quality of institutions involved in the trials, there should be an SOP describing whether and when audits of the CROs conducting the trials are planned, how audit reports are retrieved from the sponsor, how the audit team is composed.
How FGK deals with comments

- Preparation / „duplication“ of SOPs for
  - quality assurance
  - handling of documents
  - qualification and training
- Amending existing SOPs regarding tasks / responsibilities / backup of employees
- Amending the agreement with sponsors to increase involvement in information flow about
  - events relevant for safety and their reporting
  - quality and compliance of study facilities / CROs
- More staff added
How it works in practice (1)

1. Sponsors contacts FGK Representative Service GmbH.
2. Both parties sign a secrecy agreement.
3. The sponsor provides protocol, IB / IMPD.
4. FGK-RS evaluates risk of the planned study.
5. FGK-RS decides whether it assumes the role of the legal representative of the sponsor.
6. FGK sends master agreement.
7. Sponsor and FGK-RS review / discuss agreement.
8. If an acceptable text is found, both sites sign the agreement.
9. The service starts with the submission of the first clinical trial application to either an ethics committee or competent authority.

10. The sponsor sends central application documents up to 14 days before submission for review.

11. During the study, the sponsor provides copies of the complete correspondence with the ethics committee or competent authority in each study country.

12. The agreement ends with the approval of the clinical trial report by the sponsor.
Thank you for your attention

Questions ?