eSource – Regulators' perspective
eCRF, ePRO, comparison of guidance (EMA reflection paper, FDA guidance documents)

Lisbeth Bregnhøj
Medicines Inspector, GCP and GVP
Danish Health and Medicines Authority
Medicines Control & Inspection

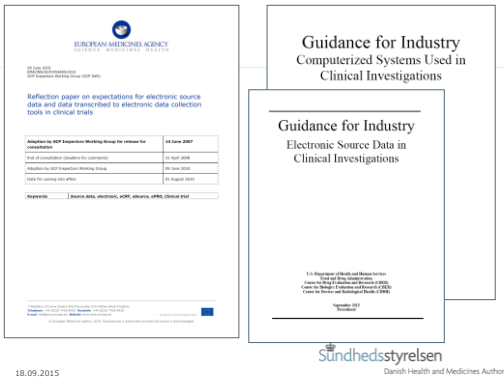
FDA and EMA papers

FDA

- **Guidance for Industry Electronic Source Data in Clinical Investigations, 2013**
- (Guidance for Industry Computerized Systems Used in Clinical Investigations, 2007)

EMA

- **Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials**



FDA and EMA papers

- There has been an awareness/information/ comment opportunity between EMA and FDA regarding the development of the respective documents
- Overall, the documents are covering a lot of the same issues and are not contradicting each other
- There are some differences, particularly in focus area and detail level

Comparison

EMA	FDA
EMA paper generally states both investigator and sponsor as responsible parties (responsibilities listed according to ICH GCP section 4 and 5) and the overall responsible party is the sponsor	FDA generally has the investigator as the responsible party and consequently deviations/findings are the responsibility of the investigator

Comparison

EMA	FDA
The GCP IWG has no preferences regarding paper vs electronic data, but there should be no loss of quality when an electronic system is used in place of a paper system	The FDA promotes capturing source data in electronic form

Examples of loss of quality when an electronic system is used in place of a paper system

- Traceability of changes to CRF pages (per field/per page)
- Independent copy of the CRF at the investigator site
- Full access to medical records sometimes prevented

Comparison

EMA	FDA
The reflection paper is centred on the 12 user requirements set by CDISC, which the inspectors have categorised into the following topics: •Creation and modification of systems •Creation, modification and transfer of data •Control •Copying •Storage	The guidance has the following sections: •Data Capture •Data review •Retention of Records by Clinical Investigators •Data Access And the guidance is intended to be used together with the FDA *guidance on Computerized Systems Used in Clinical Investigations*

Comparison

EMA	FDA
Source data should be attributable, legible, contemporaneous, orginal, accurate, complete, consistent, enduring and available when needed (ALCOA+) and must meet the regulatory requirements for recordkeeping specified in 28 different local laws. Sponsors and investigators should pay special attention to local legislation with regards to the source data going directly into the eCRF. The EHRs are first and foremost a communication tool for HCPs to ensure communication around the patient.	Source data should be attributable, legible, contemporaneous, orginal and accurate (ALCOA) and must meet the regulatory requirements for recordkeeping (specified CFR citations)

Comparison

EMA	FDA
Q&A: The intended (of source data) location should be clearly defined prior to subject recruitment. One way of achieving this is to generate a source data location list. This list should be prepared by the site and should be signed and dated by the principal investigator or by a person whom the principal investigator has assigned this task. The list should be filed in the investigator's trial master file.	Other guidance: the information provided to the FDA should fully describe and explain how source data were obtained and managed, and how electronic records were used to capture data

Example of deviation/finding

- There was no source data agreement at the site and as a consequence the monitor had done source data verification on transferred data on paper and not on the true electronic source data. ICH GCP 2.13. (including Q&A from the GCP IWG) and 5.18.4 (k) and (m) **(major)**

Comparison

EMA	FDA
The protocol should identify any data to be recorded directly into the CRFs that is considered to be source data. A detailed diagram and description of the transmission of electronic data should be provided in the protocol. The source data and their respective capture methods should be clearly defined prior to trial recruitment (i.e. in the protocol or study specific source data agreement). The sponsor should describe which data will be transferred, the origin and destination of the data, the parties with access to the transferred data, the timing of the transfer and any actions that may be triggered by real-time review of those data.	Sponsors should include (e.g., in the protocol, data management plan, or investigational plan) information about the intended use of computerized systems during a clinical investigation, a description of the security measures employed to protect the data, and a description or diagram of the data flow Other guidance: Each specific study protocol should identify each step at which a computerized system will be used to create, modify, maintain, archive, retrieve or transmit source data.

Comparison

EMA	FDA
Comment: The time for the review is probably too late as this is after the end of the trial. The review and sign off of the data by the investigator should: • allow for corrective and preventive actions for instance in case of inaccurate/incomplete data or data indicating non-eligibility of the trial subject or fulfilling the withdrawal criteria of the protocol and •ensure that only accurate data are used for the statistical analyses by the sponsor.	To comply with the requirement to maintain accurate case histories clinical investigator(s) should review and electronically sign the completed eCRF for each subject before the data are archived or submitted to FDA.

Sundhedsstyrelsen
Danish Health and Medicines Authority

Comparison

EMA	FDA
The EMA reflection paper has an added section regarding Electronic Health records. *Clinical trials can be conducted at institutions that use electronic health record systems. In that case the sponsor must assess the systems in use by investigators to determine how well they meet the requirements of GCP including those detailed in the paper. If the systems do not meet the GCP requirements then mitigating actions should be taken as necessary prior to trial site initiation. Examples where the requirements may not be met are discussed in the paper*	The guidance specifies that FDA does not intend to assess the compliance of EHRs with part 11 According to the FDA webinar on this document, the monitor will have to rely on the data presented if he or she does not have direct access to the EHR

To be continued in the afternoon

To be continued in the afternoon

Comparison

EMA	FDA
Considering the electronic source data environment it is accepted that the earliest practically retainable record should be considered as the location of the source data and therefore the source document.	When a device or instrument is the data originator (e.g., blood pressure monitoring device or glucometer) and data are automatically transmitted directly to the eCRF, the eCRF is the source…

Sundhedsstyrelsen
Danish Health and Medicines Authority

Comparison

EMA	FDA
Detailed section regarding investigator's control over data i.e. independent copy of the eCRF, specific requirements for contracts and examples of systems which would not fulfill requirements (i.e. web based eCRFs where the sponsor or somebody dependent on the sponsor is hosting the server)	The clinical investigator(s) should retain control of the records (i.e., completed and signed eCRF or certified copy of the eCRF) Other guidance: When source data are transmitted from one system to another…a copy of the data should be maintained at another location, typically at the clinical site but possibly at some other designated site. Copies should be made contemporaneously…

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Danish Health and Medicines Authority

Example of deviation/finding

- The eCRF is webbased and the database is hosted by the sponsor. The investigator does not have a contemporaneous, independent copy of his data. ICH GCP 2.13, 8.3.14 and the EMA reflection paper **(major)**

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Comparison

EMA	FDA
Comment: Direct transmission of data elements from EHR to the eCRF can only take place, if the respective EHR system is adequately validated for that purpose. Lately, a number of promising initiatives and projects have been launched in both European Member States and the U.S., but the majority of EHR systems are currently lacking the required preconditions in respect to validation and reliable protection of data privacy.	Examples of information in the FDA guidance which is not detailed in the EMA reflection paper : •Definition of data element, data element identifier, data element originator etc. with examples •A list of all authorized data originators should be developed and maintained by the sponsor and made available at each clinical site. • a specific section on direct transmission of Data From the Electronic Health Record to the eCRF •Other guidance: a list of recommended SOPs for electronic systems

Comparison

EMA	FDA
Examples of information in the EMA reflection paper which is not detailed in the FDA guidance: •Clarification that the investigator should have access (in an independent copy) at all times to all data generated in a trial relevant to patient care (questionnaires, diaries…) •Self-evident corrections performed by the sponsor •Quality control: Any transfer from paper to electronic CRF should be subject to quality control and the level of control should be justified	

Example of deviation/finding

- A major deviation was given across all three investigator sites caused by the systematic approach by the sponsor to ask investigators to sign an 'Acknowledgement of Self-Evident changes'-document stating that 'By signing this form, the Principal Investigator acknowledges that Data Management personnel may make self-evident changes to the clinical database. These changes may include, *but are not limited to the following (followed by two examples).* This wording is considered much too broad. It gives the sponsor the possibility to change (virtually undefined) investigator data without a query process. Seen in connection with the not self-evident audit trail provided by the sponsor to the investigators (which also caused the inspectors and sponsor staff numerous issues during the inspections) this is considered a **major** deviation.

Comparison conclusion

- Overall, the documents are covering most of the same issues and are not contradicting each other
- There are some differences, particularly in focus area and detail level (and maybe authority acceptance level?)
- The most important issue seems to be that the FDA does not express expectations regarding the compliance level of electronic health records and potential mitigating actions

To be continued in the afternoon

Questions?

Sundhedsstyrelsen
Danish Health and Medicines Authority