29 August 2023

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852
via online submission to https://www.regulations.gov/

RE: Docket No. FDA-2023-D-1955 “E6(R3) Guideline for Good Clinical Practice”

Dear Sir or Madam,

The International Society for Pharmaceutical Engineering (ISPE) appreciates the opportunity to comment on the above-referenced draft guidance. The document was reviewed by the Good Automated Manufacturing Practice (GAMP®) technical sub-committee ISPE which is comprised of individuals from pharmaceutical companies, suppliers, and consultants. The goal of this committee is to promote the understanding of regulations and automated systems within the pharmaceutical industry.

ISPE is a not-for-profit organization of individual members from pharmaceutical companies, contract manufacturing organizations, suppliers and service providers, and health authorities. The 21,000+ members of ISPE lead scientific, technical, and regulatory advancement throughout the entire pharmaceutical lifecycle in more than 90 countries around the world. ISPE does not take a political position or engage in lobbying activities or legislative agendas.

We appreciate the opportunity to submit these comments for your consideration. Please do not hesitate to contact me if you have any questions.

Respectfully,

Thomas B. Hartman
ISPE President and CEO
thartman@ispe.org

cc: Michael L. Rutherford, ISPE Chair

Response to a request for comments Docket No. FDA-2023-D-1955 “E6(R3) Guideline for Good Clinical Practice”

Comments submitted by the International Society for Pharmaceutical Engineering (ISPE), regulatorycomments@ispe.org

General Comments
In general, ISPE recommends adding a link to the current PIC/S guidance on the validation of computerized systems for further details on the regulatory expectations, for example in the Glossary, Computerized Validation section, starting at line 2134.

Specific Comments on the Text

ISPE indicates text proposed for deletion with ~~strikethrough~~ and text proposed for addition with **bold and underlining**.

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
Section 2.5.2, line 515ff	The investigator should document all protocol deviations and review deviations communicated to them by the sponsor.	The investigator should document **and evaluate** all protocol deviations and review deviations communicated to them by the sponsor.	The review of deviations is only mentioned for those communicated by the sponsor to the investigator. There should be an expectation that the investigator would also evaluate the impact of a particular deviation that the investigator detects.
Section 3.10, line 1102	Quality Management	Kindly consider adding references to ICH Q9/Q10 for Risk Management / Quality Management, for example in the introduction section lines 1107 or 1108.	ICH Quality Guidelines, Quality Risk Management (Q9(R1)), and Pharmaceutical Quality System (Q10) are considered relevant and helpful to the data management and clinical supplies parts of this draft Clinical guideline.

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Section or Line Number	Current Text	Proposed Change	Rationale or Comment
Section 4, lines 1813ff	Data Governance-Investigator and Sponsor	Please consider adding sub-sections for the need for defined and documented data owners and potentially data processors/handlers and/or Data Stewards	Within data governance the defined ownership of data is critical. This should be defined in the appropriate processes/frameworks.
Section 4.2, line 1854ff	*Data Life Cycle Elements*	A Data Life Cycle typically includes elements like Data Creation, Data Processing, Data Use/Reporting, Data Retention and Data Destruction. It would be good to associate the activities listed in 4.2 with these elements and add the currently missing elements of Data Retention and Data Destruction	The 'GXP' Data Integrity Guidance and Definitions from the MHRA defines it as "All phases in the life of the data from generation and recording through processing (including analysis, transformation or migration), use, data retention, archive/retrieval, and destruction".
Section 4.2.3, lines 1895ff	*Review of Data and Metadata* "It should be a planned activity, and the extent and nature should be adapted to the individual trial and adjusted based on experience during the trial."	Consider adding: It should be a planned activity, and the extent and nature should be adapted to the individual trial, and adjusted based on experience, **risk assessments, and data criticality** during the trial.	Review of data during a trial should be based on experience, risk, and data criticality in addition to "experience".
Section 4.2.4, lines 1897-1901	*Data Corrections* "There should be processes to correct data errors that could impact the reliability of the trial results. Corrections should be attributed to the entity making the correction, justified and supported by source records	Consider adding: **For these corrections, a reconstruction of preliminary results should be possible in so far as they were clinically relevant for decision-making in the trial.**	Decisions (e.g., continuation of treatment of a patient) may be driven by data that was corrected afterward; to be able to trace and audit this decision given the state of knowledge at that time, previous information should be available. This is linked to the audit trail. Larger amounts of data and aggregated

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	around the time of original entry, and performed in a timely manner."		results may confound the decision-making process.
Section 4.2.5, line 1902	*Data Transfer, Exchange, and Migration* "Validated processes or other appropriate processes such as reconciliation should be in place to ensure that electronic data transferred between computerised systems retains its integrity and preserves its confidentiality. The transfer process should be documented to ensure traceability and data reconciliation should be implemented as appropriate."	Considering the high number of systems typically involved and the high degree of outsourcing to Technology/Service providers, the data should be documented e.g., in a data flow diagram. This diagram should include references to the implemented data integrity controls like checks, reviews, reconciliation activities, etc.	ISPE suggests that such a diagram would be helpful to both regulators and sponsors.
Section 4.3, lines 1930ff	**Computerised Systems** "The sponsor should review whether the systems used by the investigator/institution (e.g., electronic health records and other record-keeping systems for source data collection) are fit for purpose in the context of the trial."	Consider adding: …in the context of the trial (i.e., validated).	If fit for purpose in the context of the trial means that those computerized systems (e.g., hospital information systems) used for EHR records and other record-keeping systems need to be validated, then it should be clearly stated, at least as a comment in brackets.
Section 4.3.1, line 1942ff	*Procedures for the Use of Computerised Systems* "Documented procedures should be in place to ensure the appropriate use of computerised systems in clinical trials	Procedures for the Use **and Maintenance** of Computerised Systems Documented procedures should be in place to ensure the appropriate use	For completeness, ISPE recommends that "maintenance" is specifically mentioned.

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	for essential activities related to data collection, handling and management."	**and maintenance** of computerised systems in clinical trials for essential activities related to data collection, handling and management **as well as system administration and maintenance.**	
Section 4.3.2, line 1946ff	*Training* "The responsible party should ensure that those using computerised systems are appropriately trained in their use."	The responsible party should ensure that those using **or maintaining** computerised systems are appropriately trained in their use.	For completeness, ISPE recommends that "maintenance" is specifically mentioned.
Section 4.5, lines 1964ff	**Validation of Computerised Systems**	Consideration should be given for example in section 4.5.1 that in GCP systems the validation often must cover: - The base system (e.g. EDC system) providing standard functionality across all studies - the study-specific setup, configuration, and/or customization Both aspects must be under change control.	The text should be expanded to help sponsors ensure all parts of the computerized system are validated.
Section 4.5.6, lines 1987ff	"Where relevant, procedures should cover the following: system design, validation, and functionality testing; release; setup; installation and change control until decommissioning."	Consider adding: Where relevant, procedures should cover the following: system design, validation, and functionality testing; release; setup; installation, **periodic review** and change control until decommissioning	Periodic review is a key process for maintaining the validation status.

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Section 4.5.10, line 2004	"The trial-specific systems (including updates resulting from protocol amendments) should only be implemented to enable the conduct of the trial by the investigator after all necessary approvals for the clinical trial have been received."	ISPE recommends that suitable text is developed that allows sponsors to progress updated international trials in those regions that have given approval without waiting for approval from all regions.	It is unclear how this will be possible for updates resulting from protocol amendments for international trials. It may be useful to clarify what the expectations would be, for example, in the following scenario: A protocol amendment for an international trial is submitted to various national ethics committees for approval, and the approvals are given at different time points. ISPE recommends that the new trial-specific system configuration be made available to the investigators where approval has been given. Waiting for approval from all authorities seems unreasonable to the investigators where approval has been given as well as patients waiting to be treated. The technical solution must allow for this situation.
Section 4.8.3, lines ff 2027	"Authorized users and access privileges should be clearly documented, maintained, and retained. These records should include any updates to a user's roles, access rights and permissions, and time of access privileges given (e.g., timestamp)"	Kindly consider adding: Authorized users, access privileges and the corresponding records should be regularly reviewed.	At least for privileged accounts, there should be a control in place.

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