13 January 2023

Submission of comments on 'Concept Paper on the revision of Annex 11 of the guidelines on Good Manufacturing Practice for medicinal products – Computerised Systems ' (EMA/INS/GMP/778340)

Comments from:

Name of organisation or individual
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Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	As IT and automation are rapidly changing and evolving, it is suggested that the revised Annex 11 should focus on key principles and objectives rather than including prescriptive details, solutions, and controls. The regulation should allow regulated companies to apply flexible and risk-based strategies based on their process understanding and knowledge of technologies, business models, and modern quality management approaches. A regulation that is as flexible and technology-neutral as possible will allow the rapid adoption of innovative technologies and approaches that can significantly benefit product quality, process control, and quality assurance, lower costs and time to market, and therefore bring great benefit to the patient and to the public. ISPE recommends regulators define their regulatory requirements in Annex 11 in sufficient detail to enable industry to adopt /apply the same to their regulated operations. ISPE recommends that the revision of Annex 11 should be aligned with other existing Chapters and Annexes of EudraLex Vol 4, for example, Chapter 4, Documentation and Annex 15, Qualification and Validation. A revision to Chapter 4 in line with Annex 11 may be necessary. The scope of Annexes 11 and 15 should be considered for	

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	clarification since some companies apply Annex 15 requirements to computer systems and some regulatory expectations are confusing.	
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2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome (To be completed by the Agency)
12-13 / 1		ISPE recommends that the revised Annex 11 should not replace the existing Q&A. The existing Q&A relating to existing Annex 11 should be updated to address any changes to Annex 11. ISPE recommends keeping the Q&A on Data Integrity.	
14-15 /2		Comment: It is important that terminology is aligned with widely used terminology and with national and international standards e.g., US National Institute of Standards and Technology (NIST) or equivalent, but also importantly, the regulation should not seek to define detailed requirements in this area but should encourage the application of relevant international standards and good practice guidance. Proposed change (if any): We suggest that the text could become: With regards to data integrity, Annex 11 will include requirements **for the complete data lifecycle** including "data in motion" and "data at rest" (backup, archive, and disposal). Annex 11 should include data lifecycle requirements.	
18-19		Comment: ISPE considers that digital transformation process is not subject to regulation. However, its application to specific product quality or related concepts would be subject to regulation. Proposed change (if any): ISPE recommends that regulation should not address the topic of digital transformation and that the guidance be updated	

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		accordingly.	
20-21		We suggest removing this point. Replacement of an existing system or process with a computerised system is covered by the change management system (change control). Regulation allows for replacing of an existing system with another. Introduction of a computerised system to replace an existing computerised system or manual process shall not compromise product quality. This could be a complex process with many approaches which, we suggest, may make guidance extremely long and complicated to cover all approaches. A robust change control process must be implemented for any changes to regulated activities.	
23		Comment: Agree with adding the term 'operate' to the list of services, but we shouldn't add 'cloud' services as technology is constantly changing. Proposed change (if any): We suggest removing the word 'cloud.'	
24-29		It is important for regulated users that changes to current Annex 11 relating to access to assurance of validation of a computerised system should apply to critical systems, which impact product quality and patient safety. It may be useful to define "critical", for example as "any system that has a direct impact on product quality via the control of a	

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		critical process parameter (CPP) or critical quality attribute (CQA)". Current 3.1 reads: "...third parties (e.g., suppliers, service providers) are used e.g., to provide, install, configure, integrate, validate, maintain..." however, line 26 is proposing that regulated users have access to the complete documentation for validation and safe operation of a critical system. ISPE considers that there are ways of assuring validation of a computerised system by a third party without regulated users having access to all validation documentation. There is no current regulation which forces suppliers to cooperate. Without that, some of the proposed changes to the guideline will prove difficult to implement. This part of the document is covered by Part 1 Volume IV EudraLex chapter 1 Pharmaceutical Quality System, and Chapter 7 Outsourced activities Regulated users should have access to the records and documentation supporting the validation of their intended use of a system and its ongoing safe operation as a GxP regulated system. Such records may include authorized third-party audit reports or certifications where the original documentation is not available to the regulated company. The validation records, documentation, and procedures directly relevant to the solution deployed to regulated company may be provided to regulatory inspectors, with assistance from the service provider as needed.	

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		Proposed change (if any): ISPE suggests keeping current scope of work definition and not superseding the existing part 1 of EU GMP's. ISPE suggests that regulated companies should appropriately assess the service providers in accordance with risk to ensure that the service provider applies adequate controls.	
36-38		Comment: Terminology and content of chapters and annexes of EudraLex Vol 4 should be aligned as appropriate with the revision of Annex 11.	
39 -42		Comment: This section is related to QRM Quality Risk management. Proposed change (if any): We suggest referring to ICH Q9 which covers fully this activity for all disciplines including IT.	
43-50		Comment: ISPE considers that the current wording requires little change. We suggest using the following proposed wording since it clarifies what is meant by the existing wording, which states "User requirements should be traceable throughout the life-cycle".	

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		"System specifications aligned with the implemented system should be maintained throughout system life-cycle and should be traceable to testing activities"	
51-53		Comment: This is suggested to further underline that output may not be in the form of traditional documents. Proposed change (if any): We suggest adding an acknowledgment that integrated automated processes and tools may be the most effective and appropriate means of achieving well-defined requirements and traceability.	
55-57		Comment: A clear definition in the revised Annex is preferred over examples. The benefit of examples is limited and there is the risk of confusing/misleading people. Proposed change if any ISPE suggest removing reference to examples and including them in a Q&A document or guidance to industry.	
58-63		Comment: Some risk-based testing should be performed for backup and restore activities. It remains unclear how the media should be validated to stay readable without reading them, and how this can be proven in advance for, say, 25 years.	

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		For very long-term storage it may not be possible to use media that is stable throughout the retention period. It should be recognized that companies may retain data beyond the regulatory retention period with the intent of using it to support a new filing. It is not impossible that the data needs to be retained for decades especially since there are regulations (e.g., for blood and tissue products) with retention requirements for 30 years. There is also increasing use of cloud storage for backup data. Proposed change (if any): We suggest replacing the text struck through below with an alternative sentence: ~~Long-term backup (or archival) to volatile media should be based on a validated procedure (e.g. through 'accelerated testing').~~ Replace with: "Long-term archival and retention processes should be defined and verified as effective."	
64-67		Comment: We believe that the regulation should define requirements only and not detailed implementation details. These can, will, and should vary widely based on circumstances. All the factors mentioned in the text will rightly vary due to individual needs and circumstances. Proposed change (if any): We suggest replacing the current text (struck through) with a simple statement that:	

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		.. .. ~~(e.g. incremental or complete), how often backups are made (all types), how long backups are retained, which media is used for backups, and where backups are kept (e.g. physical separation).~~ Replace with: "The protection of records, data, and applications should be assured through verified backup and restore processes." This ensures that backup measures and procedures should correspond to the risk of the data being backed up.	
69 - 70		Comment: We strongly support the removal of any requirement to print data for database systems in particular. For example, an MES EBR when printed runs to the thousands of pages and it is far more meaningful to review it electronically than in a report-like output. Proposed change (if any): ISPE suggests removing the printing requirement.	
71-75		Comment: ISPE recommends that the actual scope of the data audit trail is clarified as opposed to another system technical and other logs and events. As noted in Clause 24 of the concept paper, while alarms and events may require their own logs, acknowledgments, and reviews, this should not be confused with a data audit trail that	

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		captures the creation, modification, and deletion of GMP records and data. This is also consistent with US FDA 21 CFR Part 11 definition of audit trail, and other various international Data Integrity regulatory guidance documents. Logically, any data audit trail event must be about a particular subject record and an event in the history of that record. Events that are not part of the history of any particular GxP record are not data audit trail events. Industry focus for audit trail is limited to changes of GxP data. An audit trail should not log changes on users or settings by administrator functions. In most current systems there is no Audit Trail function for system configuration by administrators. For this point segregation of duties is implemented. Proposed change (if any): We suggest amending the text to: [9] An audit trail functionality which automatically logs all ~~manual interactions on GMP critical systems, where users, data or settings can be manually changed,~~ **manual interactions that create, modify, or delete GMP records and data** should be regarded as mandatory; not just 'considered based on a risk assessment'. Controlling processes or capturing, holding or transferring electronic data in such systems without audit trail functionality is not acceptable; any grace period within this area has long expired.	

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78-80		Comment: We suggest remaining aligned to the Chapter 4 statement "Where appropriate, the reason for the alteration should be recorded." There could be a risk that requiring the user to be prompted is seeking to enforce a design detail that may not be useful, relevant or necessary (i.e., not appropriate). Proposed change (if any): We suggest amending the text to: ~~for all other changes except where a value is entered in an empty field or where this is completely obvious,~~ **where appropriate**, the user should be prompted for the reason or rationale for why the change was made. ISPE suggests the removal of the example in lines 79-80 which explains how actions have to be carried out.	
81-84		Comment: ISPE considers that "privileged user" is not clear and generally understood and could include "a system administrator". ISPE kindly recommends that "privileged user" is defined.	
89 - 92		Comment: It is not possible to do a statistically significant periodic review of audit trails. Using an AQL single-sampling strategy, a database with 500,000 records would require an examination of 1250 records. Assuming 10% had changes and allowing for 2 days for QA investigation of each, that one database would require a person-year to review audit trails. Annex 11 can and should define the requirements for the provision of data audit trails by systems, but the concept or	…

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		purpose of audit trail review should derive directly from the specific GMP business process. Audit trail review must be built into the business process, and forensic review should be limited to cases with a specific reason to suspect a problem. Data audit trail review should be performed as part of any required data review, and at the same time as when that review is performed. What can be done periodically is checking that audit trail configuration and controls are in place (are they turned on, have they been turned off (and why), what is being captured, etc. The evolution of industry to digital transformation could generate more data which could make audit trail management difficult. Parameters should be assessed based on risk management. Proposed change (if any): We suggest removing the acceptable frequency, which could be too prescriptive: Guidelines for ~~acceptable frequency of~~ audit trail review and audit trail configuration review should be based on quality risk management.	
93-97		Comment: We believe this example is confusing data audit trail (deletion or modification of GxP records) with other events (e.g., error messages and other user events that belong in the system and technical logs.) If the user makes a manual change to a GxP entry in response to the error message, then it would be reasonable to reference the error message in the reason for change that they enter in the	

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		data audit trail. However, it is important that the data audit trail remains distinguishable from the event logs. Proposed change (if any): We suggest removing the example and not giving information such as how to make an audit trail:	
98-102		Comment: Sorting may be seen as a prescriptive technical requirement; in reality, it would be enough to be able to filter the entries so the audit trail can be distinguished from any event logs etc. to facilitate review and use. Proposed change (if any): We suggest amending the text as follows: Hence, as a minimum, **t<u>here should be an ability to filter entries so that relevant audit trail entries may be easily identified.</u>** We suggest not considering this point as regulation and transferring it into a Q&A clarification document or Guidance to industry.	
103-106		Comment: We agree that the total number of changes in itself is not interesting. However, a large number of changes related to the same functionality may be an indicator of a deeper issue. There is a need for addressing the mindset – the "why do we do this". People tend to misinterpret expectations and fulfill their own interpretations rather than the meaning behind (i.e., the real expectation).	

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		Configuration management is part of change management. Even if more details on it are added, it would not be good to create a new category outside change control Proposed change (if any): We suggest defining the objectives for periodic review and evaluation (i.e., checking that the system remains in compliance and **is still fit for intended use, and that critical risk controls are still effective**) and that the regulated company should define an effective mechanism for achieving this. We suggest also considering including aspects like privileges and Risk Profiles (e.g., to confirm established controls are still effective). ISPE kindly suggests emphasising that the purpose of periodic evaluations is to assess all possible indications of the system not being in control - a holistic view as opposed to the case-by-case handling during normal operation. The mechanisms for achieving these objectives should not be included in the Annex, however, could be referenced in a Q&A document. This objective can be best achieved by the use of modern configuration management tools such as a CMDB (Configuration Management Database), other automated processes, and the application of current good IT practices for Configuration Management, for example as described by ITIL, which defines Service Asset and Configuration Management (SACM) as: "The process responsible for ensuring that the assets required to deliver services are properly controlled, and that accurate and reliable information about those assets is available when and where it is needed."	

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		Manual configuration reviews are inefficient and ineffective and do not reflect current good practices.	
107-109		Comment: ISO 27001 is one possible answer to IT security. Therefore, any Information Security Management System should be acceptable. Furthermore, data confidentiality is not a GxP topic, but rather a topic of existing further legislation. This section could quote other industry standards and ongoing European Directives on Cybersecurity. Proposed change (if any): Information security management controls should be in place to manage information security risks to ensure the integrity, and availability of critical data. This clause relates as well to Clause 27 110-114. ISPE suggests merging these 2 topics.	
118-121		Comment: ISPE suggests being consistent with the wording throughout Annex 11. The term 'end users' is better understood by regulated companies than 'day-to-day users'. Proposed change (if any): Change: ~~"i.e. 'segregation of duties', that end users of a system (who have an interest in the data) do not have admin rights...".~~ to "User's rights should focus on **segregation of duties** with clear definitions."	
122-126		Comment: System Roles should be under Change control, no recurrent review is needed	

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		Proposed change (if any): Effective access management procedures should ensure user access is consistent with an end user's job role and should ensure that access is removed when no longer required.	
127-130		Same comment as above 7.2: It remains unclear how the media should be validated to stay readable without reading them, and how this can be proven in advance for, say, 25 years. We believe that the regulation should define requirements only and not detailed implementation details. These can, will, and should vary widely based on circumstances. The choice of storage media may rightly vary due to individual needs and circumstances. It would be very difficult to validate that media can be read a decade hence. The best that can be done is to follow the guidelines of the media supplier in regard to maximum lifetime, storage conditions, and media exercise. Even so, the required storage time may still exceed the media lifetime, so a refresh process may be needed. Proposed change if any: Depending on the storage media used, it might be necessary to validate that the media can be read after a certain period. **Alternatively, a process for media refresh or archive migration could be followed.**	
131-135		Comment: We cannot separate the importance of metrics, relevance, adequacy, and integrity of data from the aspect of	

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		model development, training, and optimization that involve metric selection and evaluation. Industry guidance should define the approach to validation of these evolving technologies. Proposed change (if any): ISPE suggests AI / ML should be validated for the intended use and maintained in a state of control as per any other application. These points do not need to be regulated in detail by GMPs. Keeping these systems under control by operating under pharmaceutical quality system principles and procedures e.g. on periodic reviews should be sufficient text in the Annex.	
136-140		The industry could benefit from close collaboration between regulatory agencies to ensure a harmonized approach to emerging and established guidance. An example would be a closer alignment between the requirements contained in Annex 11 and FDA's Computer Software Assurance Guidance.	

End of document