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/778340/2022*

Comments from:

Name of organisation or individual
EFPIA

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).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	We kindly recommend that terminology used should be aligned to established terminology within the IT industry where possible and other regulated standards and guidance's e.g GAMP, ISO, FDA CSA etc. EFPIA kindly recommend that specific terms, introduced and used in the document should be clearly defined to ensure clarity and considering the need to have good and consistent alignment in language and terminology with Chapter 4 and Annex 15. Specific terms that we recommend require clear definition are as follows: - Validation - Qualification - Software - Computerised System – in relation to the holistic environment e.g., not just software /hardware but business process also - Automation - Configuration Hardening - Integrated controls - Critical Systems - COTS with examples - Critical COTS - Agile/Agile principles - Configuration	

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	- Privileged users - End Users - System Administrators - Data in motion /at rest EFPIA suggests that new terms are not introduced unless they are necessary/relevant (e.g., 'Data in Motion', 'Data at rest') but to align with definitions already established in existing guidance's There is no specific reference to the use of hosted solutions, e.g., software and infrastructure as a service (SaaS/IaaS) and environments (e.g., Amazon Web Services or Microsoft Azure) - language around these types of solutions/ services is missing. EFPIA suggests that chapter 4 should be revised in parallel with Annex 11 to limit duplication and ensure alignment and consistency in approaches, concepts and terms. However, in the absence of any notification of parallel work by EMA on this, please consider in the revised Annex 11 document, guidance on the need for electronic signatures (instead of other forms of user identification/authentication), clarifying which specific or types of transaction, actions or system entries require a signature. This should be in alignment with the review/approval requirements of Ch4. Specifically, is a	

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	regulated signature necessary for all GMP 'approvals' or data entries even where the system clearly identifies the individual performing the action (e.g., data changes caught in the audit trail)? Furthermore. please consider alignment with GAMP5, 2nd edition, chapter 29 for use of Software Tools, and that systems (GAMP: 'software tools') only supporting the system life cycle are either clearly descoped or the risk-based approach for these is based on appropriate controls following good IT practices (e.g., expectations regarding audit trail and audit trail review will not automatically apply). Expectations for Software as a Service needs to be clearly described with more clarity on roles, responsibilities, and accountability e.g., there is a need to understand if it is acceptable for the supplier to fulfil an inspection request to support a regulated company's inspection. We kindly ask that EMA consider that if this becomes mandated that this could present a challenge to suppliers. EFPIA recommend that the possibility of use of the cloud should be reflected across the Annex with recognition of the new approaches, terms and language that are different from long recognise practices.	

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2. Specific comments on text

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1 (Introduction)		In the light of more and more processes being automated throughout the industry, a revision of Annex 11 embracing also modern technologies and providing guidance on what needs to be done for ensuring compliance is welcome. Nonetheless, focus should be laid on what needs to be done, providing a framework that is largely independent of specific technologies. EFPIA kindly recommend that in the update to Annex 11 there should be good and consistent alignment in language and terminology of Chapter 4 and Annex 15 .	
1-6		Comment: EFPIA welcome that this revision is a joint EU/EEA and PIC/S activity rather than the historical situation where PIC/S adopted texts originally written by EU/EEA. In the light of more and more processes being automated throughout the industry, a revision of Annex 11 embracing also modern technologies and providing guidance on what needs to be done for promoting the use of such technology while ensuring compliance is welcome. As Annex 11 predates data integrity guidance's issued from MHRA and FDA (e.g., Data Integrity and Compliance with Drug CGMP Questions and Answers Guidance for Industry), EFPIA suggest that considerations should be made to	

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		align/consider the requirements/recommendations in all these guidance's, where possible. This will help the industry which likely supply to different markets.	
12-13		Comment: see General Comments for considerations for update	
14-15		Comment: Although EFPIA agree that technical solutions and automation are preferable this should not preclude or penalise the use of manual/procedural controls where applicable or only available. EFPIA recommend Annex 11 should differentiate data integrity requirements depending on the state within the data lifecycle. Comment: EFPIA seek clarity on whether "configuration hardening" relate to "freezing" configuration settings with some type of user access controls. See also 'General Comments'.	
18-19		Comment: EFPIA agree and welcome that the document update will provide the regulatory expectations to support the industries digital transformation and use of novel technologies in a GMP environment as whole. We recommend extend this "urgent need of guidance " also to other digital and novel technologies in general, such as Digital Twins, Soft sensors in the general term, etc.	

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22		Comment: In relation to the general comment definitions, EFPIA kindly recommend that the definition of a computerised system should be updated to consider the business process and data to allow Risk Management to be applied in alignment to ICH Q9, as we suggest that a user cannot fully understand what could go wrong or what the consequence would be without the understanding of the business process or what data is critical to that process. EFPIA suggest that there is also opportunity to introduce within this chapter the capability to reduce Risk by leveraging vendor audit results.	
24-29		Comment: EFPIA agree that formal Service Level Agreements between the Regulated user and third parties must cover the need for the regulated to user to access the necessary vendor documentation to support inspection. Please consider that the regulated user may as part of validation request certain documentation, that may later be presented as part of the validation effort, but ongoing/permanent regulated user access to complete documentation from provider may not be possible. Additionally, what is requested by the regulated user should only be relevant for systems/services with direct impact on patient safety and product quality and finally if in the event the service provider makes any agreement to present and	

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		explain their documentation, the regulated user does not need to have such access at all. Comment: EFPIA suggest to also consider internal IT departments who may be service providers and where this is the case that roles and responsibilities need to be defined including all aspects of the validation. Comment: EFPIA agree with adding the term 'operate' to the list of services, but suggest a more generic term is used to express cloud services as technology is constantly changing. Comment: EFPIA suggest that Services can be included as part of COTS.	
30-35		Comment: We are concerned with the expectation to qualify all critical COTS products, since this can lead to qualify expectation of industry-well known products such as Excel. Qualification of COTS for low risk/indirect GMP systems is likely to be seen as an un-necessary burden, for low risk GMP systems the risk-based end-user acceptance testing should be adequate. The obligation of pharmaceutical manufacturers to obtain certain documentation from certain vendors is extremely challenging in the case of global software entities that provide services such as cloud services. 8(3.3) Comment: We understand that if the vendor qualifies	

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		their own tools, the expectation should be that the vendor supplies such documentation as evidence of their qualification. This would be covered in any Supplier agreement. Comment: EFPIA ask that EMA consider the use of good IT practices and Tools as part of the methods to support qualification as well as use of industry guidance's e.g. GAMP.	
36-38		EFPIA agree that the definition of validation and Qualification should be clarified as per our general comments on providing definitions of terms. EFPIA also suggest that the differences lying between the terms validation and qualification should also be addressed Utilising and aligning where possible variance guidance's e.g. GAMP 5 Ed.2 Section 19.2 EudraLex Volume 4 Part II, ASTM E2500 or other regulations and industry standards. Please consider that Computer Validation is still sometimes mis-interpreted as needing to apply the waterfall V-model approach. It would be better to emphasise that Validation should not aim to determine the software development lifecycle, rather computer validation should be focussed on identifying those patient safety, product quality and regulated data risk areas that a computerised system has associated with the business process and assuring that those	

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		risks are adequately mitigated. EFPIA agree that validation activities must focus on critical functionalities (GxP Decision making…) rather than testing minor functions. EFPIA suggest that the impact on product and patient safety should be added as criteria to decrease validation effort and function categorization. Standard, Configured and Developed could also be mentioned as assets to challenge validation effort. Proposed Change: The validation documentation and reports should cover the relevant steps of the life cycle. Manufacturers should be able to justify their standards, protocols, acceptance criteria, procedures and records based on their risk assessment and based on impact on product and patient safety. Validation activities should take a risk-based approach and focus on critical activities based on function categorization (Standard, Configured and Developed).	
43 to 50		Comment: EFPIA suggest that emphasis should be placed around the Periodic Review process for computerized systems, as this should re-evaluate all elements within the validation area, including validity of requirements and related risks. Comment: Please consider that increased use of software development tools means that increasingly User	

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		Requirements are maintained within tools. We therefore suggest removing the term "specification" to enable more digital management of requirements and helps enable the use of automated tools providing traceability. Comment: Please provide clarification of regulatory expectation for the ongoing URS. The initial URS record may not be maintained post-validation; however, user requirements defining intended use of the system shall be maintained throughout the system life cycle and be traceable to ensure satisfactory verification. Proposed change line 43 & 44: "Specified user requirements should be kept updated and aligned with the implemented system throughout the system life-cycle and there should be a documented traceability between user requirements, any underlying functional specifications and testing."	
51-53		Comment: In line with General Comments a specific definition for "agile" within this Annex is required. We kindly recommend that the guidance should provide flexibility to follow various methodologies, and associated deliverables, to demonstrate system compliance and suitability for intended use, rather than being restrictive to a particular lifecycle process/testing methodology. Proposed change: Consider adding that the project methodology followed for the implementation of the system	

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		(e.g., Agile, V-model or Waterfall) would not have to impact the compliance level of the Computerised Systems.	
54		Comment: EFPIA agree that guidelines should ground criticality around product quality as the main goal. Please also consider that it would be helpful to provide guidance on low/indirect impact systems which are often subject to excessive levels of validation - focus should be on patient risk. Note: While guidelines for critical data are welcome, this is not necessarily a topic only for computerized systems but should apply in the same manner for paper systems. Remediation measures may differ based on the associated risks, but the general concept should be the same for both electronic and paper data. Consideration should be given to aligning this with Chapter 4 also (which may need to be updated as suggested above). Comment: EFPIA ask EMA to consider also clarifying whether data' without the term 'critical' is not critical. Please also consider level of criticality along e.g. PIC/S or PDA lines? And balancing controls and level of documentation accordingly.	
55-57		Comment: EFPIA recommend that terms are aligned with other regulations/industry terms where possible, these measures 'physical and 'electronic' are also known as "physical security" and "logical security". Comment: Please consider providing clarity on 'integrity of GMP processes' which has been added – Please clarify what this means in terms of protecting these? There is already a	

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		requirement to validate to ensure fitness for intended use Comment: Also consider adding clarification on whether tools used to provide security assurances e.g. A-V, vulnerability scanning, network performance management etc do not require validation Comment: EFPIA suggest that 'Redundancy' should be described in this chapter including whether if alternate approaches are possible. Comment: There is an opportunity here to add requirements of retention period specifications based on criticality (after the definition of criticality provided as suggested in the concept paper)". Comment: EFPIA suggest to insert (basic) concepts of cyber security.	
58-63		Comment: Please consider including initial testing of restore processes in addition to periodic testing. The language around initial testing is missing. It is critical to test backup restore processes both initially and then periodically thereafter. However, some guidance on what is considered acceptable to satisfy this requirement is quite dynamic as technology and security vulnerabilities evolve – please consider this is in the update. Comment: In many cases a total restore of a system is almost impossible and of little value. Technology available to restore a single record if needed is available so the need to restore a complete batch record system adds no value (i.e.	

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		MES/SAP) and could potentially introduce more risk of the restore by having to reload data into a lower environment and address data inconsistency issues. Comment: Vendor recommendations for media longevity and storage conditions should be considered when determining the frequency/need for a periodic check of the readability of the data. Comment: It remains unclear how the media should be validated to stay readable without reading them, and how this can be proven in advance. Is this referring to a true archive solution for data where data is accessible to users, and not just sitting on a backup medium? Comment: Please consider that if a common backup platform is used for multiple systems, periodic restore testing may not be system specific. Newer technology for backup and restore provisions are used and are platform (system) independent Comment: In case of Cloud services, as part of formal agreement, proof of regular Back Up Restore must be accessible to the Manufacturer. Comment: The EMA may wish to consider adding some further guidance as to relevant data included in Back Up. It may be possible to consider some risk-based testing be	

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		performed for backup and restore activities. Comment: Please clarify what is meant 'accelerated testing' when long term backup to 'volatile media' should be based on a validated procedure– what characterises those volatile media?	
64-68		Comment: EFPIA support the general approach in sections 15 and 16, and it is acknowledged that the items in lines 65 – 67 need to be addressed within the pharmaceutical company. Nonetheless, Annex 11 should not regulate how these are implemented prescribing such items as media or interval. We caution the need to be careful this paper does not stray from principles of "what" needs to be achieved and into "how" - backup methods will vary on the technologies adopted and how technology changes. Therefore, IF this section is kept, any such requirements regarding backup expectations should be given as recommended guidance considering key variables (like risk and technology). We recommend that, any requirement on backup processes should be defined using generic wording. Proposed change line 64& 65: All backup measures and procedures should correspond to the risk of the data backed up. Comment: We recommend a differentiation is made between data and system backup and would be helpful, because the data backup is more critical than a system backup.	

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69-75		Comment: Removal of the requirement to need to print data would be welcomed - a more generic requirement to be able to present the data (in human understandable format) would be more appropriate with increased digitisation. Comment: EFPIA agree with the concept that that audit trails should be mandatory on critical process steps and associated data. However, 'GMP Critical System' is too broad a concept and will lead to blanket requirement for audit trails across every table and data object. The focus should be on critical data, not all data in critical systems. This amounts to taking a risk-based approach by making audit trail review based on risk. Proposed change: "Audit trails need to be available ... and regularly reviewed", if identified as necessary based on risk assessment. Comment: Please consider that the grace period should have considered that, for some equipment families, sometimes there are not many market options available for equipment that cover this important audit trail requirement Comment: The risk-based approach appears stricter than the risk-based approach in the enforcement discretion in FDA Part 11 Scope and Application guide – why not apply an approach as e.g. PIC/S focussing on mitigating risks by other	

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		means? Comment: Please consider to support readability, it is suggested to split handling of changes to business process data and changes to users and systems into separate sections.	
76-80		Comment: Please also consider that for audit trail, the current content states that "the user should be prompted for the reason or rationale for why the change was made. EFPIA agree, that the goal is for systems to capture the "why" in the audit electronic audit trail where possible. EFPIA would like to ensure that the "why" can be manually captured outside the system, e.g., in a logbook, if the system does not have the functionality to capture it electronically. Comment: EFPIA suggest that reconsideration is needed for enforcing the entry of a comment by the user for the change. This could become extremely inefficient, dependant on the amount of audit trailed actions. Audit trails are automatic and just happen in the background. There may be some critical actions that a comment may add value, but in most cases, vendors make this a signature action.	
81-84		Comment: Please include a definition for "privileged users and please define 'segregation of duties' as per General Comments: Please refer to general comment on definition of	

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		terms including a definition for 'privileged users', 'end users', 'system administrators' and define 'segregation of duties.	
85-88		Comment: EFPIA agree that the concept and purpose of audit trail review is inadequately described, but we are concerned that that if we write "the review should focus on..." it gives a signal not to consider (or to consider with inadequate attention) other aspects that can be critical, depending on applications. Proposed change /Suggested wording: The development of an audit trail review process must be based on the data integrity risk posed by manual changes Comment: EFPIA suggest that the audit trail review be based on risk. We see that once the purpose of the audit trail review is defined, the requirement should indicate the measurable requirements of such a review. We cannot propose elements of an audit trail review without defining the purpose. Once the purpose is defined, we can define what elements should be included. Comment: EFPIA ask that it is clarified whether changes to users' access, and system settings is mandated in scope of audit trail and the audit trail review. We recommend that this should instead be verified against approved user accesses and IT changes as part of other checks. Comment: Related to lines 76-80. if you do not assess the	

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		risk of the change and focus on the critical changes in the system this could lead to a less meaningful/focussed review. There should be allowance for 'review by exception' and the expectations for it should be clearly defined.	
89-92		Comment: EFPIA agree that guidance on frequency of audit trails is likely to be useful but important that it remains appropriately risk based as appropriate dependent on the intended use of the system. Please consider that if the system enforces review and verification of the change by a second person at the time of the change this verification should eliminate the requirement for audit trail review. Note: PDA Technical Report 84 contains risk-based tools for acceptable frequencies. This technical report can be used as source examples of how to do so. Comment: Audit trail review of pressure alarm settings at batch release? We wonder whether this is addressed by calibration status.	
93-97		Comment: EFPIA consider this section (lines 93-97) to be very detailed compared to rest of the document. If it makes sense to capture these kind of events (the one given in the example) in an audit trail, it highly depends on the criticality of the data entered and has limited value in a lot of cases. Comment: Proposed guidance is useful and clear regulatory expectation for Audit Trail is requested. 'Full set of events'	

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		should be reserved for critical data where the alterations may suggest deliberate or unintentional impact to data integrity or outcome. It would be more meaningful to ensure that ranges for data entry are defined in such a way that potentially deviating/out of specification results can be detected. Comment: Please consider that this section is currently unclear and could be misunderstood. Why e.g., a wrong formatted data entry, which is identified by the system using a format verification functionality, must be part of an audit trail?. Furthermore, there are many systems on the market that give feedback on wrong data format (e.g., letters instead of numbers) directly during input before saving of data but they do not audit trail this. A suggested approach is that data input must be automatically saved sufficiently frequent to ensure that potentially unacceptable changes can be detected. It is the criticality of the supported process (steps) and the inherent risk for data integrity breaches that determines how frequent data must be saved (e.g., per full set of observations, per subset of observations, or per entered observation).	
98-102		Comment: We recommend that we refocus on GMP critical audit trails and be readily able to identify them. Proposed change: Instead of 'sort these' should we replace with 'filter these' - 'Hence, as a minimum, it should be possible to be able to sort filter these'	
103-106		Comment: EFPIA kindly recommend that this should be	

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		reconsidered in the current state otherwise this will create unnecessary burden on the industry to conduct baseline reviews and re-evaluation of change control. This is only workable if you identify critical configuration and have a very small subset of the system to review based on risk. We recommend that this concept also needs to be built back into Risk assessment processes that identify key critical functionality that needs configuration checks or periodic re-testing can we delivered with associated functionality to enable that to happen seamlessly. We recommend that configuration review should be conducted by exception and if required following periodic review of change or incidents on the system etc where that review has highlighted an issue. Please consider aligning with recognized standards such as ISO 10007. The term configuration review does not appear in the standard. Comment: We recommend that differences should be assessed and if there are a lot of deviations from the baseline, it could be part of a risk-assessment to conduct a period review/periodic evaluation of the system.	
110-114		Comment: EFPIA suggest that this section needs to take into account risk and technologies available to restrict access e.g., multi factor authentication is unlikely to be necessary or practical for computerised lab instruments or Operational Technologies such as PLCs. Please also consider cloud	

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		services. Whilst the controls listed in this section are acknowledged security controls, not all of them should apply in all situations. Comment: EFPIA also suggest that it would be beneficial to define 'incidents' and 'problems' handling with computerised systems, specifically as they are different from deviations. Incidents and problems can arise prior to formal systems handover and therefore present less or no risk. Comment: Please consider that this section in Annex 11 is on restricted access both logical and physical. MFA would not be applicable in any capacity, e.g., badge into a computer room or access to a specific system. MFA is applicable to accessing the network. Firewalls, platform management, security patching, virus scanning, and intrusion detection/prevention are protection controls that do not control access to a system or physical computer room or data centre.	
115-117		Comment: Please consider that it could prove problematic with the journey to the cloud if for example Google or Microsoft do not agree to implement 'high degree of certainty' systems for physical access to their data centres. The focus should be on controlling access to GMP data and for companies to demonstrate how they ensure the data is adequately protected Comment: This applies to all GMP computerised systems not just 'critical systems. Please be consistent and clarify that 'GMP computerised systems' are 'critical systems. Please refer to general comments on definition of terms. Proposed change line 115 and 116: "It should be specified	

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		that authentication on GMP computerised systems should identify the regulated user with a high degree of certainty."	
116		Comment: EFPIA ask whether this implies that all pass card entries need to be replaced with multi-factor or biometric? What is considered critical enough to warrant such a changeover?	
118-121		Comment: We ask that EMA ensure consistency with the wording throughout Annex 11. The term 'end users' is better understood by regulated companies than 'day-to-day users'.	
122-126		Comment: EFPIA kindly recommend that access review frequency should be risk based Comment: This chapter appears to be mixing perspectives about security controls and Access Management process. We would recommend to divide it to have a specific chapter for access management Proposed change - Creation, change, and cancellation of access authorisations should be recorded. Access reviews must be done regularly based on risk. Procedures to grant, modify or revocate access must be established.	
127-130		Comment: EFPIA suggest including this data retrieval consideration as part of periodic system review. Comment: Please consider that suppliers of media already provide guidance on media life and readability. Comment: Please consider that while technology and storage media for archiving need to be selected to have long-term	

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		stability in accordance with current knowledge, it might be difficult to fulfil a requirement to validate such storage and to functionally demonstrate that it will really ensure functionality over time. 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? Proposed Change ' Data may be archived based on a validated system. This data should be checked for accessibility, readability and integrity. If relevant changes are to be made to the system (e.g., computer equipment or programs), then the ability to retrieve the data should be ensured and tested.'	
131-135		Comment: We welcome guidance on the validation requirements for AI / ML and agree further guidance is required, the regs are behind the technology already available. EFPIA support that 'the primary focus should be on the relevance, adequacy and integrity of the data used to test these models with, and on the results (metrics) from such testing, rather that on the process of selecting, training and optimising the models.' We suggest that the process of selecting training and optimising the models would follow scientific good practices.	
136-140		Comment: Typographical error. EFPIA recommend an editorial revision to replace Quality System Software (CSA)	

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		with Computer Software Assurance (CSA) (So that the three-letter acronym is correct) Proposed change: "[...] the FDA has released a draft guidance on Computer Software Assurance (CSA) for Production and Quality System Software (CSA).	
147-150		Comment: We agree the inclusion of AI/ML but suggest this focus on the specific risks related to those technologies and not re-invent validation basics which should still apply. Note: Clarification on what is meant by the word "acceptance" is needed. We understand it as guidance on the mentioned primary focus point in 133-134. It is important that it doesn't mean actual acceptance criteria for the model, as this is closely linked to the use case, but more acceptance means 'fit for intended use'.	
158-167		Comment: Please consider that these timelines seem rather long given that many of the revisions are intended to update the annex to current expectations and point 32 points to 'an urgent need' for guidance on AI/ML	
184-186		Comment: We question the assumption that the update will have no adverse impact, especially if considerable system updates (to include access controls as well as hardware and software) could be required. Row 184 is completely dispelled by rows 185 and 186.	

Please add more rows if needed.