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Submission of comments on Computer Software Assurance for Production and Quality System Software / 2022-09-13

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Submited by *ECA Foundation / European QP Association*

Line from* (line Nr or 0 for general comment)	Line to* (line Nr or 0 for general comment)	Section number	Comment and rationale (to go to next line within the same cell use Alt + Enter)	Proposed changes / recommendation (if applicable)
0	0	General	**Comment background** The provided comments have been prepared by an hybrid group of globally acting compliance professionals working for medical device manufacturers (Class III) as well as in the pharmaceutical GMP, GDP, GCP, and GLP areas as well as in research and development, such as: - Quality Assurance representatives, incl. IT QA - Engineers, in particular automation and process control - Laboratory scientists, in particular in charge of the qualification of laboratory equipment - IT department members - Software suppliers - GxP compliance consultants and auditors - ...	
0	0	General	**"Computer Software Assurance" vs "Computerised System Validation"** If the guidance shall have an impact outside of the medical device sector, the guidance title shall be reconsidered since it contradicts the definition of a "computer**ised** system" based on PIC/S PI 011-3, section 6.2. CSV does not cover software quality only but takes a holistic approach including, beside the computer, the controlled process, the related procedures, and the personnel. These elements are not or only very limited addressed in the guidance possibly causing confusion for the readers. Additionally, in the case of "*production and quality system computer systems*" the compliance scope cannot be reduced to "computer software" but must cover the computerised system in its entirety. Furthermore, in 2022, since most manufacturing and laboratory equipment are usually computer-controlled, CSV should be emphasised instead of artificially segregating equipment (21CFR820.70(g)) and automated processes (21CFR820.70(i)). The current guidance content could be misundertood by the industry causing a compliance decreasing and a control loss for production and quality system computer systems. *See comments to lines 20-22*	Please clarify the compliance scope - i.e. CSV - for "*production and quality system computer systems*"
0	0	General	**CSA guidance vs current industry thinking** While the GAMP Community proactively endorsed CSA (see GAMP Good Practice Guides "*Data Integrity by Design*" and "*Enabling Innovation*", as well as GAMP 5 Second Edition) based on discussions and presentations made by the Agency during the last 5 years, the current guidance draft does not accurately reflect major recommendations provided by GAMP - e.g. "Critical Thinking", "Leveraging Supplier Involvement", ... - although these recommendations and key-concepts represent a significant way to improve the overall compliance maturity and to limit at the same time the necessary compliance effort.	Please emphasise, where appropriate, guidance alignment with current industry thinking as formalised by GAMP.
0	0	General	**CSA vs General Principles of Software Validation** The choosen approach to amend the GPSV by superseding Section 6 and replacing it with the CSA guidance is highly unfortunate since it causes confusion for the readers. It would be clearer and better to issue a new version of the GPSV with a revised content, including a possible formal scope extension (GCP, GDP, GMP, GLP). *See comments to lines 28-31*	Please consider to update GPSV instead of creating a new guidance.

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0	0	General	**Testing taxonomy** Based on the comments related to V - C (lines 400-432), the reference to IEC/ISO 29119-1 destroy any efficiency improvements. The testing taxonomy proposed by IEC/ISO 29119-1 is inadequate in a regulated engineering context.	Please suppress the reference to IEC/ISO 29119-1
0	0	General Appendix A	**Appendix A: Risk management** At the time Q9 is being revised, it is higly questioning that the "risk-based approach" discussion in Appendix A is only focused on "Risk Analysis" (deliberately?) ingnoring principles and process described in Q9. The only focus on "risk analysis" instead of Risk Management represents a significant regression in terms of compliance and efficiency.	Please fully revise Appendix A, advocating for and emphasising importance and relevance of sound science-based risk management.
15	18	I	**Guidance applicability** While Footnote #1 mentions that this guidance has been prepared in collaboration with CBER, CDER, OCP, and ORA, the guidance only refers to 21CFR820, not considering in any way pharmaceutical cGMP (21CFR211) or GLP (21CFR58). Additionally the guidance is not aligned with the current PIC/S GMP - PE 009 - in particular with Annex 11.	Please consider a scope extention formally covering GMP, GDP, GCP, and GLP. Please ensure consistency with Annex 11 to the current version of PIC/S PE 009.
16	18	I	Even if "*computers and automated data processing systems used as part of medical device* ***production*** " are mentioned, the proposed examples in Appendix A are only related to "non-production" systems.	Please add examples for a process control system used in manufacturing and for a system controlling a laboratory equipment used for Quality Control activities.
20	22	I	For "*production and quality system computer systems* " the compliance scope cannot be reduced to "*computer software* " but must cover the computerised system in its entirety; i.e. CSV. *See General comments*	Please clarify the compliance scope - i.e. CSV - for "*production and quality system computer systems* "
24	26	I	*See comments to lines 15-18*	Please consider a scope extention formally covering GMP, GDP, GCP, and GLP or explicitly exclude everything outside of Medical Device sector.
28	31	I	Is it a real simplification to replace 3 (GPSV section 6) pages with 20+ pages (CSA guidance)? Why not simply updating the GPSV? *See General comments*	Please consider to update GPSV instead of creating a new guidance.
43	57	II	**Background** See general comments and comments related to Guidance applicability	Please clarify the compliance scope - i.e. CSV - for "production and quality system computer systems"
68	68	II	"*e.g., automotive, consumer electronics* " Comparing regulated medical devices with less regulated industry sectors can be very dangerous. The safety expectations are not similar. Past experience has shown that the transfer of industry practices from less regulated sectors to stricter regulated sectors (aircraft, healthcare) can lead to safety catastrophes.	Please remove the mentioned examples. If industry sectors outside of healthcare sector should be mentioned, aircraft would be more appropriate.
70	71	II	"*medical device manufacturers have expressed a desire for greater clarity regarding the Agency's expectations* " This objective is not achieved with this guidance draft, since the document causes more confusion than brings clarification.	Please consider to update GPSV instead of creating a new guidance.
76	82	II	The statement provided in this paragraph contradicts the GPSV which already covers the software life cycle. Additionally, it contradicts as well the present document which has a strong focus on testing and related documentation. Indeed testing alone is not the guaranty for software quality and relibility, in this case, why are testing and testing documentation finally in the main focus of this guidance?	Please consider to update GPSV instead of creating a new guidance.
84	92	II	Risk-based approach to compliant GxP computerised systems has been consistently formalised by GAMP 5, First Edition, in 2008. The previous remarks to the effective scope of this guidance document remain valid for this paragraph.	The proposed guidance should simply refer to the GAMP 5 guides (first as well as second edition) instead of rewording the topics to be considered. Please clarify and - possibly - extend the guidance scope to pharmaceutical GxP activities, processes, and systems.

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95	97	III	**Scope** These recommendations are already available in multiple industry good practice documents. It is not helpful to ignore them instead of refering to them.	Please refer to current industry good practice guides.
99	105	III	The statement provided in this paragraph shows again that it would be better to revise and improve as appropriate GPSV instead of creating an additional guidance with a confusing limited scope.	Please consider to update GPSV instead of creating a new guidance.
114	115	IV	**Computer Software Assurance** "*Computer software assurance is a risk-based approach for establishing and maintaining confidence that software is fit for its intended use.* " This definition is finally a risk-based approach to CSV ! Why must a new acronym be created for finally saying the same than before? Such ambiguity is not helpful and confuses already many people in the industry.	Please consider to update GPSV instead of creating a new guidance and avoid to create and to use new and ambiguous acronyms.
115	120	IV	"*Because the computer software assurance effort is risk-based, it follows a least-burdensome approach, where the burden of validation is no more than necessary to address the risk.* " GPSV provides a similar statement in section 2.3.	Please consider to update GPSV instead of creating a new guidance.
122	130	IV	What this paragraph describes with long sentences is finally the definition of e-compliance : - Fitness-for-the-intended-use (Qualification/validation) + maintained under control during operation until retirement	
126	130	IV	Leveraging supplier involvement (who ever the supplier is: external or internal supplier) is one of the 5 key concepts proposed by GAMP 5.	Adovcate for leveraging supplier involvement and for the conditions for such leveraging.
132	135	IV	*See comments to lines 122-130*	
138	140	V	Unfortunately, neither process control systems used in manufacturing nor analytcal equipment used for quality control are part of the examples provided in Appendix A.	Please add process control system and analytical equipment in the examples provided in Appendix A.
142	218	V - A	**Identifying the Intended Use** "Intended use" is already mentioned 32 time in GPSV ! The need for an additional guidance is not obvious.	Please consider to update GPSV, if necessary, instead of creating a new guidance.
160	172	V - A	Considering software used to backup GxP relevant data being a system supporting quality, it is not possible to assess such a being "low risk"; with regards to ALCOA+, such a system is critical. Obviously if we detect that the tools does not work as inteded then we can react and repeat the backup activities; however if the probability of detection is low, the possible loss of data could affect quality, patient safety, as well as compliance.	Please provides examples to clarify the situation
183	183	V - A	FDA recognizes that software used in production or the quality system is often complex and comprised of several features, functions, and operations… "several" suggests a small number - reword for clarity.	FDA recognizes that software used in production or the quality system is often complex and comprised of multiple featuresand functions.
183	184	V - A	"FDA recognizes that software used in production or the quality system is often complex and comprised of several features, functions, and operations..." This sentence introduces the frequently repeated phrase 'features, functions and operations' which is unhelpful as these terms are not consistently defined across the broad range of business, analytical and process control computerised systems. This phrase is also not aligned with GAMP 5 Second Edition terminology which consistently uses 'features and functions' and specifically 'function' throughout the risk management sections.	For clarity it is suggested that 'function' be used throughout the document in place of 'features, functions and operations'.
184	Footnote 5 below	V - A	The footnote defines features, function and operation in an arbitrary way (see comment related to line 184). Suggest reword for clarity.	Software features and functions support the operation of each computerised process. For the purpose of this guidance 'function' refers to a software function and is not to be confused with a 'device function'.

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193	206	V - A	"For example, a commercial off-the-shelf (COTS) spreadsheet software may be comprised of various functions with different intended uses..." Spreadsheet systems are a weak example in regulated environments as they are inherently non-compliant with ERES expections. Suggested revision of this paragraph is provided.	For example, a commercial off-the-shelf (COTS) data management software may be comprised of various functions with different intended uses. When utilizing the basic input functions of the COTS software for an intended use of documenting the time and temperature readings for a curing process, a manufacturer may not need to perform additional assurance activities beyond those conducted by the COTS software developer and initial installation and configuration. The intended use of the software, “documenting readings,” only supports maintaining the quality system record and poses a low process risk. As such, initial activities such as the vendor assessment and software installation and configuration may be sufficient to establish that the software is fit for its intended use and maintains a validated state. However, if a manufacturer utilizes built-in functions of the COTS system to create custom formulas that are directly used in production or the quality system, then additional risks may be present. For example, if a custom formula automatically calculates time and temperature statistics to monitor the performance and suitability of the curing process, then additional validation by the manufacturer might be necessary.
193	206	V - A	Within a regulated context where data integrity represents one of the compliance key-stones, an example based on spreadsheet is fully inappropriate since the use of spreadsheets for performing regulated activities is the source of multiple non-compliances. Even only for visualising a document (worksheet), a spreadsheet tool can deliberately or not deliberately truncate the content, possibly causing inappropriate GxP decisions. GAMP 5 Appendix S3 provides a clearer discussion and a more consistent compliance view on this topic.	*Or alternatively (to the comment above)* Suppress the reference to spreadsheets Suppress this discussion since it causes more confusion than guidance.
208	214	V - A	Finally this paragraph aims to enforce a "risk-based approach focused on the effective intended use". Everything is only verbiage confusing the reader.	
221	245	V - B	**Determining the Risk Based Approach** "Risk" respectively "risk-based" is already mentioned 150 time in GPSV ! The need for an additional guidance is not obvious. ICH Q9 provides a consistent approach to Quality Risk Management and it could be easily referred to in addition to ISO 14971.	Please consider to update GPSV, if necessary, instead of creating a new guidance. If the guidance scope could be extended to pharmaceutical GxP, Q9 should be referred to as well.
247	290	V - B	The proposed binary approach to risk management based on "*high process risk*" and "*not high process risk*" causes a weak granularity hindering the elaboration of an effective scalable and commensurate approach to compliance. It finally contradicts the efforts jointly provided by regulators and industry during the last 20 years for efficiently achieving compliance.	Please reconsider the risk granularity, avoiding a binary approach to risk management.
247	290	V - B	Following the proposed examples of process risks, how would you classify a system used for managing the calibration records? - High process risk? - Not high process risk?	Please consider to provide more nuanced examples
271	277	V - B	The proposed discussion regarding "not high process risk" is doubtful and could lead to inappropriate risk decision making. "*Intended use*" should be clearly identified; considering that failing to perform according to the intended use is a contradiction to compliance approach. Probably, the idea is to consider some "anciliary" system functionalities not having a direct impact to the supported process and to the generated records being less critical than the core functionalities defining the intended use.	Please revise or suppress this discussion

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271	291	V - B	The examples mentioned in this discussion are very questionning since in several cases they could not be considered as being "*not high process risk*". (see in particular comments to lines 286-290). It is highly dangerous to try to deemphasise the process relevance of CAPA, change management or monitoring processes. What would an FDA inspector say during an inspection if a regulated company would miss to correctly apply changes to a manufacturing recipe of an analytical method just because the system supporting change management was considered having "*not high process risk*"?	Please revise or suppress this discussion, incl. the mentioned examples not forgetting that the intended use of systems supporting quality relevant activities is finally the key-criteron for "*high*" or "*not high process risk*".
286	290	V - B	The example related to "*alerts when an exception occurs in an established process*" is highly unfortunate, since it represents a "high process risk".	See comments to line 271-291
374	496	V - C	**Determining the Appropriate Assurance Activities** This section is mainly based on the terminology and philosophy defined in IEC/ISO 29119-1. Within the software engineering and software testing communities, IEC/ISO 29119-1 does not represent a consensus. IEC/ISO 29119-1 is definitively not well fitting with GxP expectations. - The testing terms proposed by IEC/ISO 29119-1 are already highly confusing (see the discussions within the industry since the early CSA phase regarding "scripted" and "unscripted" testing. - The related formalism is heavier than the industry does based on an efficient approach to testing and verification. - Implicit expectation that every types of test must be formally documented. However within the scope of engineering activities during the project phase, exploratory testing is common and not subject to formalism. - Only "robust scripted testing" considers traceability to the requirements (see below)	Please suppress the reference to IEC/ISO 29119-1 and propose a less confusing terminology. IEC/ISO 29119-1 has been revised in 2022 (the document refers to the version released in 2013).
413	419	V - C	It is not meaningful to explicitely mention "exploratory" tests as being part of the overall test and compliance strategy, since exploratory tests are part of the engineerig activities (sandbox) prior finalising the specifications and starting with the formal verification and compliance activities. This point represents one of the biggest issue raised by this guidance. Formally integrating exploratory tests in the compliance activities will cause an unnecessary increasing of effort instead of simplifying (as claimed) the compliance activities.	Please remove exploratory tests from this guidance.
421	432	V - C	Confusion between scripted and unscripted when talking about the limited scripted testing => difficulties to decide on the appropriate assurance activities.	Please suppress the reference to IEC/ISO 29119-1 and propose a less confusing terminology.
425	427	V - C	While most testing activities based on so-called documented "*unscripted testing*", the reference to IEC/ISO 29119-1 causes that only "*robust scripted testing*" shall provide traceability to the requirements and support auditability. PIC/S PE 009, Annex 11 requires "*User requirements should be traceable throughout the life-cycle*". It would be a significant regression to require in the future the industry to only make "robust scripted testing" in order to secure requirement traceability. The guidance purpose is to streamline compliance activities, the reference to IEC/ISO 29119-1 destroy this objective in a very efficient way.	Please suppress the reference to IEC/ISO 29119-1 and propose a less confusing and more flexible terminology.
434	442	V - C	"*risk-based testing*" is not meaningfully and efficiently achievable as long as the definitions provided by IEC/ISO 29119-1 are kept in this guidance.	Please suppress the reference to IEC/ISO 29119-1 and propose a less confusing and more flexible terminology.
444	446	V - C	"*When deciding on the appropriate assurance activities, manufacturers should consider whether there are any additional controls or mechanisms in place throughout the quality system that may decrease the impact of compromised safety and/or quality if failure of the software feature, function or operation were to occur*." This sentence could be better expressed - see suggested revision - for clarity.	"When deciding on the appropriate assurance activities, manufacturers should consider what existing upstream or downstream quality system controls or mechanisms which mitigate the impact on safety and/or quality should failure of the software function occur."

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444	453	V - C	These paragraph is finally advocating for "computerised system validation" based on the definition of a "computerised system" provided by PIC/S PI 011, section 6.2. Finally - and fortunately - CSV remains the main compliance objective.	
444	482	V - C	The main question is "*does the industry need this CSA guidance?*" since this section widely provides a reasonable statement. Nevertheless please consider the proposed improvements (rewording or suppression) related to lines 444-482, see below.	Please consider to update GPSV instead of creating a new guidance.
458	460	V - C	"*For some lower-risk software features, functions, and operations, this may be all the assurance that is needed by the manufacturer*."	This statement is not needed - and lacks clarity - suggest delete.
466	468	V - C	" … *these controls can serve as additional mechanisms to detect and correct the occurrence of quality problems that may occur if a software feature, function, or operation were to fail to perform as intended.In this example, the presence of these controls can be leveraged to reduce the effort of assurance activities appropriate for the software*."	This statement is a repetition of for example lines 444-449 - suggest delete.
470	474	V - C	This part could cause confusion since it mixes assurance activities related to the project phase and assurance activities reletaed to operation.	A better structure would be meaningful.
477	477	V - C	"The use of Computer System Validation tools…" Use of the term "*Computer System Validation*" here could be confusing - see suggest revision	"The use of tools supporting software development and system life cycle activities …"
488	488	V - C	"… by leveraging vendor validation records." Validation remains the responsibility of the regulated company. See suggested revision	" … by leveraging vendor records e.g. quality management system records and software development life cycle records (software installation, configuration, testing etc) …"
495	496	V - C	"Manufacturers may leverage any of the activities or a combination of activities that are most appropriate for risk associated with the intended use." Minor revision for clarity suggested.	"Manufacturers may leverage any of the activities, or a combination of activities, that are most appropriate for the mitigation of identifed risks associated with the intended use.
524	524	V - D	The rows of Table 1 are not presented in order of rigor - this may be confusing or unhelpful to practitioners.	Suggest to resequence - as per Appendix S2 in ISPE GAMP RDI Good Practice Guide - Data Integrity by Design.
524	525	V - D	**Table 1 : Examples of Assurance Activities and Records** After reading this table, it is not clear how the proposed approach simplifies the validation activities compared to the GAMP guide. It was expected FDA would support that regulated users could rely on the results of the software test and verification activities performed by the supplier, as long as the outcomes of the supplier audit results provide sufficient confidence in the supplier's QMS.	
533	534	V - D	Spreadsheet: The monitoring of environmental parameters can have a direct impact on the product quality and patient safety. Additionally it is very unlucky to provide an example based on spreadsheet in a compliance guidance. See comments to lines 193-206	Please clarify the example and remove the mention to spreadsheet.
535	556	V - D	"*The manufacturer conducted rapid exploratory testing of specific functions used in the spreadsheet to ensure that analyses can be created, read, updated, and/or deleted*." If this data is used for a regulatory purpose (e.g. investigation of a non-conformance) it is in the scope of 21CFR11 (and other data integrity related guidances) which require a complete record according to ALCOA+ principles - deletion is not permitted. See comments to lines 193-206 See comments to lines 413-419	Please clarify the example and remove the mention to spreadsheet.

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535	556	V - D	We are moving to avoid using spreadsheets for GxP activities and we argue in this guidance by taking this kind of tools?	Please remove the mention to spreadsheet.
537	538	V - D	See comments to lines 413-419	Please remove exploratory tests from this guidance.
584	586	V - D	"Manufacturers have expressed confusion and concern regarding the application of Part 11, Electronic Records; Electronic Signatures, to computers or automated data processing systems used as part of production or the quality system."	This is a repetition of the statement at 69 -72. Suggest delete.
597	599	V - D	"In the context of computer or automated data processing systems, for computer software used as part of production or the quality system, a document required under Part 820 and maintained in electronic form would generally be an “electronic record” within the meaning of Part 11 (see 21 CFR 11.3(b)(6))." Vague statement when regulation is clearer - see suggested revision.	In the context of computer or automated data processing systems, for computer software used as part of production or the quality system, a document required under Part 820 and maintained in electronic form is e an “electronic record” within the meaning of Part 11 (see 21 CFR 11.3(b)(6)).
611	617	Appendix A - Example 1	**Example 1: Non conformance Management system** **Table 2: Computer Software Assurance Example for a Nonconformance Management System** Electronic signature - 21CFR11 - requirements are more complete than the risks identified in this table! (link to document, access management, training, etc…). The corresponding column content "*Establishing the appropriate record*" seems to be neither complete nor focused on the identified risks.	Appendix A shall be fully rewritten ensuring clarity and consistency of the proposed examples. It would be very appreciate that examples related to manufacturing equipment and quality control equipment would be proposed.
622	623	Appendix A - Example 2	**Example 2: Learning Management System (LMS)** **Table 3: Computer Software Assurance Example for an LMS** Failure of these features, functions, or operations to perform as intended would impact the integrity of the quality system record but would not foreseeably compromise safety. As such, the manufacturer determined that the features, functions, and operations do not pose high process risk. If the training concerns an operator working a critical process then we have high risk that the GmP requirements are not fullfiled . A non performed training for an operator could have an impact on Data Integrity requirment ALCOA + (Contemporaneous not respected)	Consider the risk evaluation otherwise we are lost
627	628	Appendix A - Example 3	**Example 3: Business Intelligence Applications** **Table 4: Computer Software Assurance Example for a Business Intelligence Application** "The software is intended to better understand product and process performance over time, in order to provide identification of improvement opportunities." Statement reworded for clarity.	The software is intended to provide information regarding product and process performance over time, in order to facilitate the identification of improvement opportunities."
631	632	Appendix A - Example 3	**Example 3: Business Intelligence Applications** **Table 4: Computer Software Assurance Example for a Business Intelligence Application** Clairfy the scope of the system: Data Integrity vs trending or analysis.	Rework example 3