20 October 2008

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SUBMISSION OF COMMENTS ON PROPOSED REVISIONS TO CHAPTER 4 AND ANNEX 11 OF VOLUME 4 EU GUIDELINES TO GOOD MANUFACTURING PRACTICE

ISPE is pleased to provide comments on the above Guidelines, compiled by GAMP Community of Practice within ISPE. We support the timely revision to Chapter 4 and Annex 11 in recognition of technology changes and industry developments. In summary, our main observations are:

1) The application of a risk-based approach can be extended within current regulatory expectations. Companies should be able to define their approach so long as they can justify it. We have suggested additional areas where a risk-based approach can be adopted.
2) Levels of controls for electronic records should be practical and commensurate with risk. Specific system features determining how systems should operate should not be specified. It is the responsibility of companies to demonstrate how they meet GMP requirements. We have identified some proposed changes that would benefit from flexibility in this regard.
3) Avoid terminology that links requirements to specific types of computerised system. We have suggested amendments that would make requirements independent of technology employed.

We would much appreciate that the comments and issues detailed in the document are addressed.

Yours sincerely,

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GAMP Analysis of Draft GMP Chapter 4 on Documentation

Draft 4, 30th September 2008

Key Philosophical or Strategy Issues
This is a GMP document, but these principles apply across all GxP areas. In some places the scope is stated as GxP, not GMP.
Several of the examples are not technology-neutral. There is a danger that they will rapidly become obsolete.
Quality Risk Management principles could be applied more generally. There are many blanket statements about data definitions, audit trails, and other requirements that may only be appropriate for critical systems. The term "risk" and the concept of documented, justified, risk assessments are absent from the document.
The requirements would be clarified if the main body of Chapter 4 addressed requirements for all records. Any additional requirements unique to electronic records or unique to paper records should be clearly defined in separate sections.
The draft uses the terms "must", "should", and "may", and other equivalent terms throughout. There is a lack of clarity as to what is a requirement, a recommendation, a good practice, or an example approach.
There is a danger that examples may be confused with requirements. It is recommended that examples, especially those involving technology, be removed from this document.

Page, section, paragraph	**Relative Importance**	**Key Concerns with Explanation of Position**	**Proposed change**
P2 §3	H	The footnote states that an EDMS "may be required for critical electronic records and other documents" The regulations should not dictate or recommend solutions or technologies. If a firm can come up with a secure alternative, an EDMS should not be a requirement.	The quoted text should be removed. GMP requirements should not recommend specific technology solutions.

Page, section, paragraph	Relative Importance	Key Concerns with Explanation of Position	Proposed change
P3 §4.1(b)	H	"Records include the raw data which is used to generate other records." This needs to be qualified. This is relevant in the case of QC records that are used to generate a certificate of analysis. It is not, however, realistic for individual tablet weights used to derive a weight distribution for a batch. The only relevant data there are the distribution curve and the number of samples that fall outside the limits. Companies should be able to define the regulated record *and be required to justify it.* This becomes very significant enabling Review by Exception. For example, if there is a validated process that ensures excursions generate alarm reports, the absence of alarms should be adequate to demonstrate control. Please consider also the note at the top of P5 of the draft regulation, and footnote 2.	Delete the quoted statement, and replace it with: *"The raw data must be defined in the context of the records."*
P3 §4.1(b)	M	"For an electronic document management system (EDMS), all forms of electronic documentation system elements have to be defined, including embedded or linked programs (e.g. objects, hyperlinks or macros) and metadata." It is not appropriate for a regulation to describe requirements for a specific technology, application, or system type. Technology innovations could affect the way in which the requirements are met, making specific statements obsolete.	Recommend deleting this sentence. The rest of the statement is technology neutral and is appropriate.

Page, section, paragraph	Relative Importance	Key Concerns with Explanation of Position	Proposed change
P3 §4.1(b)	L	The reference to Annex 11 Section 5 does not seem relevant. Annex 11 is invoked anyway without reference by virtue of inclusion in GMP requirements.	Delete reference.
P3 §4.1(b)	M	"The programmable processes acting upon electronic documentation elements need to be understood, well documented, validated and controlled within a secure information management system. "Programmable processes" are determined not just by the specific application but also by the links, controls, permissions and settings for the totality of the computerised system's functionality." This passage adds unnecessary complexity. Annex 11 is invoked anyway without reference and covers validation expectations.	Suggest this passage is removed.
P4 §4.7	H	"Changes made to electronic records should be visible both on-screen and on printouts. It should be possible to view the prior entry as space on a computer screen is limited." This is requirement is unclear as it stands. It is unclear whether this refers to visibility on screen or is an audit trail type requirement. On-screen display will not be practical in all circumstances. There is no benefit if change history can be demonstrated another way. On-screen display may be detrimental to the reading of routine	Suggest change to: "It must be possible to verify whether changes have been made to *critical* electronic records."

Page, section, paragraph	Relative Importance	Key Concerns with Explanation of Position	Proposed change
		operational information. It should be adequate to have an audit trail and the need for an audit trail should be decided based on risk. If data cannot be changed, or if the risk is low, the need to know whether data has been changed may not warrant the extensive technical and/or administrative costs.	
P4 §4.9	L	"…detailed procedures relating to the system in use should be available and the accuracy of the records checked." Although this text already exists in GMPs it is open to interpretation that there needs to be a manual check to audit records for accuracy. It should be enough to show that the system generates accurate records (via validation) and that they are adequately controlled, safe, and secure (via good system management processes). This would better reflect current regulatory practice during inspections.	Recommend clarifying statement to read 'and the accuracy of records verified by manual or validated automatic checking'.
P4 §4.9	L	"The result of entry of critical data should be independently checked." This requirement should only refer to manual entry of critical data. This would better reflect current regulatory practice during inspections. A validated computer system should be an acceptable check of critical data entry.	The result of manual entry of critical data should be independently verified by either manual or electronic means.

Page, section, paragraph	Relative Importance	Key Concerns with Explanation of Position	Proposed change
P4 §4.9	M	"…only authorised persons should be able to enter or modify such data and there should be an audit trail i.e. a record of changes and deletions, (even at System Administrator level)." At some level there will always need to be someone who has a level of access that can manipulate and audit trail. The best that can be accomplished is that such access is limited to persons independent of the use of the application.	Change to: "…a record of changes and deletions. Persons with access to modify or delete the audit trail must be independent of the system users/owner, and must record all such actions according to established change control processes."
P4 §4.9	H	"A systematic, accurate, secure audit trail is required." Audit trail requirements should be dependent on the nature of the record and the risk associated with it. Audit trails are an appropriate control for batch record entries, but not for environmental monitoring data (assuming data locked and can not be changed) or for training records (low risk). 100% audit trailing would have significant effects on system performance and costs.	Change to: "For critical GxP records a systematic, accurate, secure audit trail is required. The need for an audit trail should be based on a documented, justified, risk assessment."

Page, section, paragraph	Relative Importance	Key Concerns with Explanation of Position	Proposed change
P4 §4.9	M	"Data and records (e.g. batch records) and other Quality System related documentation elements, electronically stored, should be protected by validated duplication, or back-up and transfer on magnetic tape, disks, microfilm, paper or other validated, secure media to avoid loss or damage of data." This requirement should be technology neutral and hence media types are inappropriate to mention. Also media cannot be validated; it is more appropriate to require media to be "secure".	Suggest replacing text with "For data and records (e.g. batch records) and other Quality System related documentation elements reference should be made to Annex 11 sections 14 and 15 regarding data storage, back-up, migration, archiving and retrieval"
P4 §4.9	M	Relating to back-up: "Audit trails also need to be maintained for such transfers." Audit trail carries some specific meaning related to electronic records and electronic signatures which is not what is intended by this statement.	Suggest changing to "*Records* need to be maintained for such transfers."
P4 §4.9	L	This document references PIC/S guidance PI-011-3. As a general rule, it is our belief that regulations should not reference a guidance document which is not controlled in a synchronised manner with that regulation.	Suggest remove reference.

Page, section, paragraph	Relative Importance	Key Concerns with Explanation of Position	Proposed change
P4 §4.9	M	"Note: Where a validated process is continuously monitored and controlled, then automatically generated reports may be limited to compliance summaries and exception/ out-of-specification (OOS) data reports as required by specifications derived from process analytical technologies detailed in approved marketing authorisations." We support enabling PAT but suggest clarification needed to avoid technology bias.	Suggest replace text with "Where a validated process is continuously monitored and controlled, then automatically generated reports may be limited to compliance summaries and exception/ out-of-specification (OOS) data reports as required by specifications detailed in approved marketing authorisations."

Explanation of Content in Table

"Item with Reference Line #": Provide a short definition of the item linked to significant locations in the document where it occurs.

"Relative Importance": Select the level of importance to your organisation from the list below.

H = A critical issue which we feel strongly about

M = A minor point which we note but is less important

L = An editorial point which could help to clarify the text or remove and error

"Key Concerns with Explanation of Position": a short, bulleted list of the specific concerns your organisation has with the item.

"Proposed Change": your suggested modification

GAMP Analysis of GMP Annex 11 on Computerised Systems

Draft 4, 30th September 2008

Key Philosophical or Strategy Issues
This is a GMP document, but these principles apply across all GxP areas. In some places the scope is stated as GxP, not GMP.
Several of the examples are not technology-neutral. There is a danger that they will rapidly become obsolete.
The draft links control with risk in many but not all cases. Risk management considerations should be applied consistently throughout.

Page, section, paragraph	**Relative Importance**	**Key Concerns with Explanation of Position**	**Proposed change**
Principle	L	"This annex applies to all forms of computerisation used in connection with regulated activities, including process control, documentation and data-processing systems. It also covers development, selection, validation and use of systems. For documentation, the requirements of GMP Chapter 4 shall also be considered."	Add "retirement" to the scope statement.
Principle	L	"the manufacturing authorisation holder/ purchaser may need to assess the development/ validation evidence for the product at the supplier. (See also clauses 1, 2 and 6 below.)"	Should be clauses 1,2, and 5.

Page, section, paragraph	Relative Importance	Key Concerns with Explanation of Position	Proposed change
P3 §3.1	M	"The call for up to date listings of systems and their GxP functionality may lead some firms to go into too much detail on the functionality. Also, as noted above, this is a GMP guideline. "	Suggest amend phrase to read "The call for up to date listings of systems and their GxP purpose…"
P3 §3.1	L	The footnotes are missing.	Replace missing text.
P3 §3.1	L	The term "validation schedule" implies another document not currently defined.	Recommend stating that "The validation status of each system must be indicated"
P3 §3.2	H	"For the validation of bespoke or significantly customised computerised systems there should be a process in place that assures the formal assessment and reporting of quality and performance measures for…" Not all bespoke systems require this level of attention (e.g. simple spreadsheets).	Suggest amending text to read "For the validation of bespoke or significantly customised computerised systems there should be a risk-based process, e.g. as described in ICH Q9 and Annex 20…"

P3 §3.2	L	"…for all the life-cycle stages of software and system development, its implementation, qualification and acceptance, operation, modification, re-qualification**,** maintenance,…" If change control process followed then're-qualification' can be avoided.	Propose delete "re-qualification"
P3 §3.2	L	" (With regards to customised systems, the above described controls are required for customisation aspects and their impacts on the whole system)"	Recommend deletion as this text does not add any clarity as currently written
P3 §3.4	M	"Validation documentation should include change control and error log records generated during the validation process." While there should be change management during the validation process, it is unclear why these records are singled out for attention. We believe these are covered in Section 3.3.	Recommend deleting Section 3.4.
P3 §3.5	H	"Evidence of challenge testing should be included, particularly system parameter limits, data limits and error handling." The depth of testing should be based on a documented, justified risk assessment.	Suggest adding text to end "The depth of testing should be based on a documented, justified risk assessment."
P3 §3.6	M	"In fitting with best practices for risk assessment and change management…"	Recommend changing to read "In fitting with best practices for quality risk management and change management…"

P4 §3.7		The entire section 3.7 is too specific and too technical.	Recommend deleting the entire section.
P4 §3.7 first bullet	L	If section 3.7 is not deleted: "Mechanisms for ensuring data integrity in terms of accuracy and reliability (e.g. macros for check of data logic; table field design etc)" Terminology used reflects current technology. Requirements should be independent of technology i.e. technology-neutral).	Remove the parenthetical addendum.
P4 §3.7 last bullet	M	If section 3.7 is not deleted: "On line archiving of data where applicable" Archiving strategy should not be in question here. Only integrity of the archived data should be discussed.	Suggest deleting text.
P4 §3.8	L	"The calculations should be secured in such a way that formulations are not intentionally or accidentally overwritten." Inappropriate use of word 'formulations' which could be misconstrued in this industry.	Suggest replace 'formulations' with 'formulae'. .
P4 §3.8	M	"Formulations should also be protected from accidental input of in appropriate data type (e.g. text in a numeric field and or a decimal format into integer field)." Inappropriate use of word 'formulations' which could be misconstrued in this industry.	Suggest replace 'formulations' with 'formulae'.

P4 §3.8	M	"Formulations should also be protected from accidental input of in appropriate data type (e.g. text in a numeric field and or a decimal format into integer field)." "Protected" may be taken as requiring a logical check, but in most spreadsheets input of alphabetic data to a calculation will result in an error message; that should be enough; "in appropriate" should be "inappropriate".	Suggest change to "Accidental input of an inappropriate data type should be prevented or result in an error message."
P4 §4.1	M	Requirements for the system inventory are too prescriptive. Further, this is covered in Section 3.1	Recommend deleting 4.1
P4 §4.2	M	"Current specifications should be available (including diagrams as appropriate). They should describe the required functions of the system, any modularity and their relationships, its interfaces and external connections, system boundaries, main inputs and outputs, main data types stored, handled or processed, any hardware and software pre-requisites, and security measures."	This statement is too specific. Recommend replacing this entire paragraph with: "Documentation should be available that describes the functionality of the system and the way it is used."

P5 §5.2	L	“Documentation supplied with Commercial Off-The-Shelf products should be reviewed…” COTS is a concept that is not widely agreed/well understood within the industry.	Suggest replacing with “software applications”. Even documentation supplied by internal developers should be reviewed.
P5 §5.3	H	“Quality system and audit information relating to suppliers or developers of software and systems implemented by the manufacturing authorisation holder should be made available to inspectors on request” It is unclear whether “audit information” is intended to mean detailed information or a general summary It is the policy of many firms that supplier audit reports are not shared with regulators.	Potential rewording depending on intent see key concern opposite
P5 §6.1	M	“Critical systems should be designed and protected to ensure that data and files cannot be changed without appropriate authorisations and with immutable electronic logs recording changes made even at the highest level of access, such as System Administrator.” The use of the word critical needs clarification.	Change to “Systems which have been determined by risk assessment to be critical…”
P6 § 9.2	M	This section requires a second check for critical process steps, but does not allow for the check to be electronic. A second check should be allowed to be electronic, as it is in 9.1.	See 9.1

P6 §10.1	H	“Consideration should be given to building into the system the creation of a complete record of all entries and amendments (a system generated "audit trail")”	Suggest change start of sentence to read “If the risk level warrants, consideration should be given…”
P7 §10.1	H	“For example if a relevant electronic record is created using a number of data fields, all these data fields need to be linked within the audit trail.” A record may have non-critical information that doesn’t need that level of control. For example, a sales rep drops samples with a physician, and enters some sales related notes in the record of the visit. The critical data elements are the date, what drug was supplied, how much, and the physician’s electronic signature. The rep’s note to visit him again in 3 weeks is not relevant and need not be audit trailed if he later edits that to 4 weeks.	Recommend revising the statement to say: “Risk assessment should used to decide which data elements in a record, if any, require an audit trail.”

P7 §11.1	L	Electronic signature must “include the time and date that they were applied.” The time is not a requirement for paper records; only the date is. This can cause significant confusion with global systems. The rules should be the same for paper and electronic signature. Only systems where time is critical, e.g. a batch record system, should require a time stamp in addition to a date stamp.	Clarify rationale behind timestamp.
P7 §11.2	L	“Country specific national legislations may apply to the requirements and controls for electronic records and linked electronic signatures, or identities.” This is applicable beyond this individual item.	Recommend deleting this sentence.
P7 §11.2	H	“Printed copies of electronically compiled and electronically signed documents should be traceable via printed links to the original electronic transaction.” This would be appropriate for reports from the system. Such reports may not always be a capability, and it might not be possible with screenshots.	Coupled with the previous comment, delete all of paragraph 11.2.

P7 §11.2	L	Reference to non-existent section 20.	Amend text.
P7 §12.1	L	“These should include provision for the evaluation of the impact of the change on product quality and data and system integrity, scoping any necessary validation work, reporting, reviewing approving and implementing the change.” This addresses specifics of risk assessment and is not necessary.	Recommend deleting this sentence, as the first sentence in this section is adequate to describe the requirement.
P7 §13.1	H	“Printouts of records must indicate if any of the data has been changed since the original entry.” This is an impractical and very onerous. If evidence of whether data has been altered is required the audit trail can be consulted.	We strongly recommend this requirement be deleted.
P7 §14.1	L	“Data should be secured by both physical and electronic means against wilful or accidental damage, in accordance with item ‘4.9’ of the Guide”	There is no 4.9 in this Annex. Please clarify to what “The Guide” refers.
P7 §14.1	H	“The storage media used should have been subjected to evaluation for quality, reliability and durability by or on behalf of the manufacturing authorisation holder.” The quality and reliability of storage media is understood and does not need further evaluation. Storage media, both magnetic and other, are commodity items and are robust and reliable.	Recommend deleting this sentence.

P7 §14.1	M	"If changes are proposed to the computer equipment or its programs, the above mentioned checks should be performed at a frequency appropriate to the storage medium being used." Time not change is usually the driving factor for the need to check/exercise/refresh storage media.	Recommend replacing this text with the following: "At a frequency appropriate to the storage medium being used, manufacturer-recommended maintenance procedures should be carried out. If changes are proposed to the computer equipment or its programs and a data migration is required, archived records must be in scope as appropriate (see also §15.2.)"
P7 §15.1	H	"Integrity and accuracy of back-up data should be checked during or on completion of the back-up process." Some checks maybe possible as part of the back-up process, but in general the back-up process should have been covered in validation, so that in-process or post-process checks can be minimized.	Recommend the following: "Integrity and accuracy of the back-up process should be verified during validation."
P7 §15.3	L	"Backup, archiving, retrieval and restoration (recovery) practices need to be defined, tested and established in accordance with the manufacturing authorisation holder's QMS, ISMS and risk management requirements." Business continuity is a key consideration too.	Suggest changing text to read "…QMS, ISMS, business continuity, and risk management requirements."

P7 §16.1	H	"The time required to bring the alternative arrangements into use should be minimal and appropriate for a particular system." The term "Minimal" is unclear, and if risk is low, the business may choose to apply recovery resources to higher priority problems.	Recommend the following: "The time required to bring the alternative arrangements into use should be based on risk and appropriate for a particular system."
P9 §19	L	It is unclear why this section appears in Annex 11. This describes data requirements more than computer system quality requirements. Regulations relating to the QP are described in Chapters 1 and 4.	Recommend deleting this section.

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