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Ref: EU Guidelines to GMP,
Medicinal Products for Human and Veterinary Use,
Draft Annex 11, Computerised Systems
(08 April 2008, comments due 31 Oct 2008)

Dear Sabine and David:

PDA is pleased to have the opportunity to provide comments on the revisions to GMP Annex 11, Computerised Systems. Our comments were prepared by a group of member experts in this field after considerable discussion. Our comments are attached in the requested EMEA format.

In general the proposed revisions are acceptable and helpful. We have proposed some changes in order to make the guidance more useful. We particularly appreciate the following aspects of the revision which comport with international harmonization:

- Support of risk-based validation processes
- Validation measures which increase the quality and safety of critical systems.

If I can be of further assistance, please feel free to contact me, or our Director of Regulatory Affairs, Jim Lyda at: lyda@pda.org.

With very best regards,

Georg Roessling, PhD
Senior Vice President
PDA Europe

Cc: Corbin, Levy, Dana, Lyda

**PDA COMMENTS ON**
**EMEAGUIDELINES TO GOOD MANUFACTURING PRACTICE,**
**MEDICINAL PRODUCTS FOR HUMAN AND VETERINARY USE**
**Draft Annex 11, Computerised Systems**

| Section # | Existing Wording | Proposed Change | Rationale |
|---|---|---|---|
| **Page 1; Principle** | | We suggest a general opening paragraph be added noting that the level of detail applied to the requirements outlined in this document should be based on a documented analysis of how the system is used, the level of complexity and risk assessment. | This recommendation consistent with GAMP 5; March 2008 |
| Section 1 | **1. Risk Management** | Include a section 1.2 on risk management as follows: "Risk to product quality and patient safety should be managed throughout the system lifecycle, including: design, construction, qualification and modifications thereafter. The extent of the risk management should be commensurate with the scope and complexity of the system. | The existing text mentions only risk assessment which is part of risk management. |
| Section 3.1 | The manufacturing authorization holder's … together with up to date listings of systems and their GxP functionality. | Change wording to: "…with up to date listings of systems and their intended use." Remove "…their GxP functionality/" | Consistent with GAMP 5 |
| Section 3.1 | The validation status of each system should be clear from the Validation Schedule. | The validation status of each system should be clear from the list of validated systems. | Clarity. The term Validation Schedule is not generally used or defined. |
| Section 3.1 | … the manufacturing authorization holder's documented risk assessments. [i, ii] | Remove i and ii or add reference text | The references for these two superscripts are missing |

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| Section # | Existing Wording | Proposed Change | Rationale |
|---|---|---|---|
| Section 3.2 | For the validation of bespoke or significantly customized computerized systems, there should be a process … | Change to read: The validation of bespoke, configurable or significantly customised computerised systems should be based on risk assessment and there should be a process... | This section implies the same level of effort is required for all bespoke systems. There should be a risked-based approach. Configurable systems should also be included based on GAMP 5. |
| Section 3.3 | The validation documentation should cover all the relevant steps … as required. | Remove the word "all" in the first sentence and replace "as required" with "based on risk assessment". | Section 3.3 needs more clarification. The phrase "as required" is not clear and it allows validation representatives to reach their own conclusions as to what is required and what is not. The recommended changes are consistent with GAMP 5. |
| Section 3.5 | With regard to the testing phase of the validation process | Change first sentence to: "If automated testing tools are used..." | Clarification. |
| Section 3.7 | Mechanisms for ensuring … (e.g. macros for check of data logic; table field design, etc.) | Remove (e.g. macros for check of data logic; table field design etc) | Guidance need not reference specific solutions. The general statement is sufficient. |
| Section 3.7 | On line archiving of data where applicable. | Add new sentence to the end of this clause, "…of data where applicable. The archive process should not affect data or data integrity." | The accuracy of the archiving process and the integrity of the archived data are the issues. |
| Section 3.7 | NA | Validation of database systems is required for quality and regulatory systems. The extent of validation should be based on risk assessment and best practice. | Consistent with GAMP 5 |

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| Section # | Existing Wording | Proposed Change | Rationale |
|---|---|---|---|
| Section 3.8 | The calculations should be secured in such a way that formulations are not … Formulations should also be protected … | Change "formulations" to formulae | The word "formulations" in pharmaceutical/cosmetics industries, formulation has very specific meaning. |
| Section 3.8 | Formulations should also be protected …into an integer field). | Reword to read "Accidental input of an inappropriate data type should be prevented or result in an error message" | "Protected" may be taken as requiring a logical check. |
| Section 4.1 | The inventory should mention the site and purpose …system. | Reword the sentence to read, "The inventory should mention fitness for purpose of the authorised computerised system." | The word "site" is useful but not necessary. Use of "purpose" or "fit for intended use" should be consistent throughout the document. |
| Section 4.2 | Current specifications should be available … and security measures. | Delete the first two sentences and replace with the following: "User Requirements Specifications should be available. These should be developed internally before the purchase of the software. These requirements will define how the software will be used and what the requirements of "fit for intended use (purpose)" are. The requirements may also be based on documented risk assessment and GxP impact." | These documents are the supplier's product design and usually proprietary. Manufacturers will not provide proprietary information that would jeopardize their product. |
| Section 5.2 | Computerised systems should be designed … user requirements are fulfilled. | This section requires clarification, especially with regard to COTS. | As written, this section is confusing and without clearer understanding, we are unable to offer any specific recommendation for change. Perhaps this could be clarified in the context of GAMP 5. |

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| Section # | Existing Wording | Proposed Change | Rationale |
|---|---|---|---|
| Section 5.3 | Quality system and audit information relating to suppliers … | Suggest changing wording to: "Quality system and general summary of audits performed relating to suppliers …" | Audits of external hardware and software suppliers are typically part of internal auditing programs. These are performed under confidentiality agreements with suppliers. Specific audit findings cannot be shared without the auditee's permission. |
| Section 6.1 | Critical systems be designed and protected … | Change to, "Critical systems, based on risk assessment, should be designed and protected …" | Proposed change is consistent with GAMP 5 |
| Section 6.1 | "Critical systems …recording changes made even at the highest level of access, such as System Administrator." | Remove: "…recording changes made even at the highest level of access, such as System Administrator." | This is a stipulation for the system manufacturer, not the customer. The lack of this (common in many systems today) is a risk assessment factor for the customer |
| Section 7.1 | Before a new, replacement or upgraded computerized system …, it should have been thoroughly specified, documented, validated, tested and approved … | Change wording to read: specified, documented, tested, approved, and validated... | The proposed change clarifies the wording to be consistent with the usual order of events, i.e. validation.. |
| Section 8.5 | **NA** | Add the sentence "The system should be able to detect invalid or altered records. " | Consistent with normal practice. |

| Section # | Existing Wording | Proposed Change | Rationale |
|---|---|---|---|
| Section 10.1 | The system should enable the recording of … need to be linked within the audit trail. | Delete the identified text and replace with the following,<br><br>"The system should enable the recording of:<br><br>• Unique identity of authorized operators modifying, altering, creating, confirming critical data based on risk assessment.<br><br>• Reason for change<br><br>• Accurate history of changes<br><br>• Date, time and time zone<br><br>Leave the last two sentences as per the existing wording." | Clarification |
| Section 11.1 | NA | Suggest including a separate section 11.3 on hybrid systems, including clarification that using e-signatures or using hybrid is OK.<br><br>• 11.3 (1) e-signatures may be used on e-records.<br><br>• 11.3 (2) e-records may be printed and signed with a handwritten signature.<br><br>• 11.3 (3) Bio-metrics may be used with e-signatures. | This section talks about electronic signatures and hybrid systems. A handwritten signature is not an electronic signature applied to paper. |

| Section # | Existing Wording | Proposed Change | Rationale |
|---|---|---|---|
| Section 11.2 | Printed copies … (See also Section 20, below). | Remove the sentence starting with "Printed Copies...". and the reference to Section 20. Move the remaining sentence from this section to the **Principle** section of this Annex 11. | Electronically signed records are the official record. The remaining sentence is a general statement that is not applicable to just "signatures", it covers both records and signatures. There is no Section 20 in this version of Annex 11. |
| Section 13.1 | NA | If the system provides system-generated audit trails that can be printed upon request, then users should not be required to provide additional printouts. | Elimination of redundant requirements |
| Section 14.1 | " … in accordance with item '4.9' of the Guide …"<br><br>The storage media … the manufacturing authorisation holder.<br><br>If changes are proposed…. The storage medium being used. | Clarify the reference to 4.9<br><br>Delete the sentence starting with "The storage media..." and replace it with the following: "Evaluate what media is most suitable and what storage interval is required for recovery of data on the media selected."<br><br>Suggest removing the sentence that starts with "If changes are proposed..." | There is no Section 4.9 in this Annex.. This appears to refer to Section 4.9 in revised Chapter 4 of the EU GMP Guide..<br><br>Storage media is a commodity. Stating that the data must be recoverable for the required storage interval would require firms to purchase media from reliable vendors.<br><br>Change is not the issue here. The characteristics of the various media are well documented |

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| Section # | Existing Wording | Proposed Change | Rationale |
|---|---|---|---|
| Section 15.1 | Integrity and accuracy of back-up data … of the back-up process. | Remove the sentence beginning with "Integrity and accuracy..." and add the following:<br>"The integrity and accuracy of the back-up data should be tested as part of the initial validation of the system and re-evaluated as required. This interval would be determined by the firm based on risk analysis activities." | The original wording implies testing during or after every back-up, which occurs daily in many large firms. Our proposed change is consistent with risk management principles. |
| Section 15.2 | This data should be checked … and integrity. | Remove the sentence beginning with: "This data should be..." | Storage media should not have to be evaluated for quality, reliability and durability. The characteristics of the various media are well documented. |
| Section 15.3 | Backup, archiving, retrieval and restoration … authorization holder's QMS, ISMS and risk management requirements. | Change to read as follows: ..." QMS, ISMS, business continuity, and risk management requirements." | Clarification |
| Section 16.1 | For the availability …, provisions should be made … or alternative system).<br><br>The time required … for a particular system. | Instead of the word "provisions" clarify it with the following: "there should be a risk-based business continuity plan with systems availability being defined in terms of risk."Change "The time required…" to: "The time required to bring the alternative arrangements into use should be appropriate for a particular system and the business process it supports. | Consistent with current standard practices |