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31 October 2008

Enterprise and Industry Directorate-General
European Commission
B-1049 Brussels
Belgium
BY EMAIL TO entr-gmp@ec.europa.eu and GMP@emea.europa.eu

Re: Draft Annex 11 "Computerised Systems"

Dear Sir/Madam,

The Biotechnology Industry Organization (BIO) appreciates the opportunity to provide comment on the draft Annex 11 "Computerised Systems" to the EU's Guidelines to Good Manufacturing Practice (GMP) for Medicinal Products for Human and Veterinary Use. BIO represents more than 1,200 biotechnology companies, academic institutions, state biotechnology centers and related organizations in more than 31 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products.

GENERAL COMMENTS:

The revised Annex 11 will enhance the ability of manufacturing authorisation holders to ensure the smooth introduction of computerised systems into manufacturing without a decrease in product quality, process control or quality assurance. Our specific comments below are directed toward clarifying the language of the draft Annex to further enhance its utility for manufacturing authorization holders.

SPECIFIC COMMENTS:

Section	Comment and Rationale	Proposed change (if applicable)
Section 2.1	The term "closest co-operation" could be misinterpreted to imply a decrease in the independence of oversight by Quality Assurance.	We recommend the insertion of the following sentence at the end of this section: "For quality assurance staff, the level of co-operation must be consistent with the performance of independent oversight."
Section 3.1	It is not clear what is meant by "Validation Schedule". Footnotes i and ii were not included in this document.	We recommend replacing the second sentence "The validation status of each system should be clear from the Validation Schedule" with the sentence "The manufacturing authorisation holder must be able to identify the validation status of each system". We recommend that these footnote numbers be deleted or that the relevant footnotes be provided in the text.
Section 3.2	The term "significantly customized" is not clear.	We request that examples of "significant customization" be provided. We recommend the following examples: multiple changes beyond interfacing; use of software outside the scope of vendor-defined capabilities.
Section 3.3	The term "complexity assessment" is not defined, and it is not clear how such a complexity assessment would relate to the risk assessment.	We recommend deletion of the words "and complexity" in the third sentence.

Section	Comment and Rationale	Proposed change (if applicable)
Section 3.5	The assessment should be documented; the wording of the first bullet state this clearly. The wording of the second bullet should clarify that the choice of specific types of challenge testing to be included should be based on a risk assessment.	We recommend that the wording of the bullets in this section be revised as follows: "- Automated testing tools used for validation purposes should have documented assessments of ~~for~~ their adequacy. - Evidence of challenge testing ~~should be included, particularly~~ such as system parameter limits, data limits and error handling should be included based on a risk assessment."
Section 3.7	The sixth bullet may be interpreted to require testing to allow for future growth of the database, even if future growth is not anticipated. This may lead to unnecessary expenditure of resources. Instead, testing should be performed across the intended usable range of operation.	We recommend that bullet six be reworded as follows: "Load testing (to include the current needs and as appropriate to support future growth of the database)"
Section 4.1	The suggested scope of the inventory, i.e. "all computerized systems" is very broad and could be interpreted to include systems that are irrelevant to GMP. The scope of the inventory should be clarified to include only GMP-relevant systems.	We recommend that the first sentence be reworded as follows: "An inventory, or listing, of all GMP-relevant computerised systems is essential."
Section 5.3	In order to maintain third party confidentiality, "audit information" made available to inspectors must be limited to basic information (such as dates and names of auditors) that demonstrate that an audit occurred. We note that if the availability of audit information is not limited, the result may be that the audit process is constrained and improvement at third party vendors is hindered.	We recommend that this section be reworded as follows: "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~~,~~ – when doing so is consistent with the need to protect third party confidentiality and does not undermine the audit process – as supporting material intended to demonstrate the quality of the development processes."

Section	Comment and Rationale	Proposed change (if applicable)
Section 6.1	The use of shared passwords may be compatible with "irrefutable recording of the identity of operators".	We recommend deletion of the text in parentheses regarding passwords so that the second sentence reads as follows: "Data and document management control systems should be designed to ensure the integrity of data and irrefutable recording of the identity of operators entering or confirming data as well as the routing and source of data captured or received automatically."
Section 8.2	The current wording unnecessarily limits the ways in which access to applications (etc) may be controlled. Simplified wording would suffice.	We recommend that this section be reworded as follows: "Access to applications, folders, files and data should be controlled".
Section 8.4	The license holder should retain flexibility to manage document hierarchy in a manner that best achieves tracking and audit trailing for security purposes.	We recommend that the words "Within the ISMS" be removed and that the section begins "There should be a defined procedure that enables tracking ..."
Section 9.1	Given the definitions of Qualification and Validation in the Glossary to the GMP Guidelines, available at http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/glos4en200408.pdf, the word "validated" in the second sentence should be replaced with "qualified".	We recommend the following revision to the second sentence: "This check may be done by a second operator or by ~~validated~~ qualified electronic means."
Section 10.1	Any alteration of data – whether those data are "critical" or not – should be documented.	We recommend that the word critical be deleted in the first and second sentences: "The system should enable the recording of the unique identity of operators entering or confirming ~~critical~~ data. Any entry or alteration of ~~critical~~ data should be authorised and recorded with the reason for the change."

Section	Comment and Rationale	Proposed change (if applicable)
Section 11.1	This section should address alteration of records and signature validity.	We recommend addition of a second sentence, "In either case, a process should be in place to assure that the record does not change after signature."
Section 11.2	There is no Section 20 in this document.	We recommend that the text in parentheses "(See also section 20, below)" be removed.
Section 12	This section does not address the integration of change management with configuration management.	We request the addition of language to describe the integration of change management with configuration management.
Section 13.1	We disagree that "Printouts of records must indicate if any of the data has been changed since the original entry". While this may sometimes be appropriate, in most cases it is not necessary that printed records show both original and corrected entries if readily available electronic records maintain any changes to data after the original entry. Within the electronic record changes should be identified and footnoted with the date and reason for the change.	We recommend adding text to the first sentence so that it reads "Printouts of records must indicate if any of the data has been changed since the original entry, or indicate the location of an electronic record that maintains changes to data after the original entry".
Section 15	Although the title of this section is titled "Back Up; Migration; Archiving; Retrieval", data migration is not specifically discussed in this section.	We recommend the removal of the word "Migration" in the title of this section, or the addition of text to address migration.
Section 15.3	Manufacturing authorisation holders may not address backup, archiving, retrieval or restoration (recovery) practices in an Information Security Management System (ISMS).	We recommend that "ISMS" be removed from this section, so that it reads "…authorization holder's QMS~~, ISMS, and~~ or risk management requirements."

Section	Comment and Rationale	Proposed change (if applicable)
Section 16.1	Some computerised systems may be "critical" although they do not support regulatory or lifesaving processes. The section should allow for this possibility.	We recommend rewording the first sentence as follows: "~~For the availability of computerised systems supporting critical regulatory or lifesaving processes, p~~Provisions should be made to ensure continuity availability of critical computerised systems ~~of support for those processes~~ in the event of a system breakdown (e.g. a manual or alternative system). The identification of critical computerised systems should be based on risk."
Section 17.1	Not all system failures and data errors have the potential for negative impact on system operation or data integrity. Also, Incident Management may include preventive actions.	We recommend that the first sentence be reworded as follows: "Where there exists a potential for negative impact on system operation or data integrity, s~~S~~ystem failures and data errors should be tracked, recorded, and analysed, and corrective and preventive actions should be implemented as appropriate."
Section 18.1	The first sentence can be clarified.	We recommend revision of the first sentence as follows: "When outside agencies, suppliers, or other parties are used to provide, install, configure, integrate, validate, maintain or modify a computerised system or related service or for data processing, ~~there should be~~ a formal agreements must exist between the manufacturing authorization holder and any third parties, and these agreements should include~~ing a~~ clear statements of the responsibilities of those~~at~~ outside bodies~~y~~."

CONCLUSION

BIO appreciates this opportunity to provide comment on the draft Annex 11 "Computerised Systems" to the EU's Guidelines to Good Manufacturing Practice (GMP) for Medicinal Products for Human and Veterinary Use, and we would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/s/

Sara Radcliffe
Vice President, Science & Regulatory Affairs
Biotechnology Industry Organization