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

RE: Draft Annex 2: Manufacture of Biological Medicinal Products for Human Use

Dear Sir/Madam,

The Biotechnology Industry Organization (BIO) appreciates the opportunity to provide comment on the European Commission's (EC's) Draft *Annex 2: Manufacture of Biological Medicinal Products for Human Use.* BIO represents more than 1,150 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products.

GENERAL COMMENTS

We welcome this revision of Annex 2 to *Volume 4 - Medicinal Products for Human and Veterinary Use: Good Manufacturing Practice* (the GMP Guide), and we appreciate the incorporation of the newly published concepts from the International Conference on Harmonisation's (ICH's) guidelines Q8 (*Pharmaceutical Development*)and Q9 (*Quality Risk Management*). We also welcome the establishment of cGMPs for advanced therapy medicinal products (i.e., gene therapy, somatic cell therapy medicinal products and tissue engineered products).

However, we interpret the proposed revised Annex 2 to create an inconsistent set of requirements for biological (drug) substance (BDS) manufacture, by separating the cGMP requirements for BDS into three different documents:

- Part II of the GMP Guide (*Basic Requirements for Active Substances used as Starting Materials*), currently available at http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/2005_10_03_gmp-partii-activesubstance.pdf
- ICH Q7 (*Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients*), currently available at http://www.ich.org/LOB/media/MEDIA433.pdf, and

- the proposed revised Annex 2 (*Manufacture of Biological Medicinal Products for Human Use*), currently available at http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/2005_10_03_gmp-partii-activesubstance.pdf

This approach of having different sets of requirements is unnecessary, and is of particular concern to us because the proposed revised Annex 2 appears to be far more restrictive for BDS than the other two documents. We suggest that any revised Annex 2 address only aspects of manufacture for biological medicinal products (indeed, the title of the proposed revised Annex 2 does not reflect the addition of BDS to the content of the annex, but rather reflects the annex's previous applicability to biological medicinal products only). The requirements for BDS manufacture of monoclonal antibodies and therapeutic proteins made using recombinant technology (cell culture/fermentation) should remain incorporated into a revised Part II of the GMP Guide that is aligned with ICH Q7. The requirements for BDS for vaccines and advanced therapy medicinal products should be addressed (preferably) in a revised Part II of the GMP Guide under a new and separate section, or (less preferred) in a completely new and separate Annex.

Additionally, in many of the new requirements of the proposed revisions to Annex 2, industry is expected to prepare documented risk assessments to justify decisions. This is consistent with implementation of ICH Q9. However the proposed revised Annex 2 does not distinguish among the different types of products addressed in the Annex, and it appears that similar practices are expected for all product categories. It is not consistent with ICH Q9 to apply similar practices to advanced therapy medicinal products which have no approved example product (e.g. gene therapy) with those products with have several decades of history as commercially available products (e.g. monoclonal antibodies and therapeutic proteins made using recombinant technology). Furthermore, the control strategy(ies) proposed for manufacture of drug substance and manufacture of drug product do not appear to be clearly differentiated, though the potential risk to public safety may not be equivalent.

We are also concerned that guidance related to risk minimization is separated into the three different documents. Some of the documents contain requirements that are more restrictive than others. This will lead to confusion in implementation by industry as well as in inspection by regulatory agencies. For example, the controls associated with the production of live virus vaccines, inactivated virus vaccines or pathogenic organisms clearly should be more restrictive than the controls associated with production of monoclonal antibodies or recombinant therapeutic proteins in E. coli or CHO cells. The revised draft annex, however, does not appear to distinguish among the product types. Shared equipment and operation of multi-product facilities has been common practice for the later product types, and to suggest that "dedicated facilities and equipment" should be considered is neither science-based nor practical.

Therefore we suggest the following for your consideration:

1. The title and content of Part II of the GMP Guide should be revised to align with and reflect the intent of ICH Q7 and include requirements for all APIs and BDS. We note that at the present time, the industry interprets and applies the principles and cGMP guidance from ICH Q7 to be applicable to all active substances, both chemical active pharmaceutical ingredients (APIs) and BDS). Unfortunately, the current title and content of Part II of the GMP Guide does not align with ICH Q7 (that is, according to its title Part II of the GMP Guide is currently applicable only to "Active Substances used as Starting Materials").

2. As part of the revision in described in point 1 above, the requirements for BDS for vaccines and advanced therapy medicinal products should be broken out into a new and separate section within the revised Part II of the GMP Guide. Alternatively (but less preferably) these requirements could be addressed in a new and separate Annex.
3. If these changes to Part II of the GMP Guide are made, the revised Annex 2 should continue to pertain only to biological medicinal products, as its current title suggests.

SPECIFIC COMMENTS

PROPOSED CHANGES TO EXISTING TEXT OR NEW TEXT		
Line number[1], paragraph number, or page number	**Comment and Rationale**	**Proposed changes (if applicable)**
Title page 2	The title of the proposed revised Annex 2 (*i.e.*, *Manufacture of Biological Medicinal Products for Human Use*) does not match the document's proposed content. The title suggests that the document's content is specific to biological medicinal products only, while the proposed content has been expanded to include BDS.	We suggest that the title of the revised Annex 2 remain the same, while the requirements for BDS be removed and either be included in a revised Part II of the GMP Guide, or in a new and separate Annex that is specific to advanced therapy medicinal products only (as described in our comments below).
Scope page 2	The scope of the proposed revised Annex 2 has been expanded to include BDS in addition to biological medicinal (drug) products. As a result, the scope of the proposed revised Annex 2 overlaps with that of Part II of the GMP Guide and ICH Q7 as follows: • The scope of the proposed revised Annex 2 is described as follows: *Biological medicinal products obtained from the sources and prepared by the methods listed in Table 1 will fall under the scope of this annex … For biological substances, the appropriate section of this Annex should be read in*	We suggest the scope of a revised Annex 2 be described as follows: "*Biological medicinal products obtained from the sources and prepared by the methods listed in Table 1 will fall under the scope of this annex. … Biological drug substances are subject to the applicable sections of Part II of the GMP Guide*.

[1] Where available

	conjunction with that given in Part II of the GMP Guide. (p. 2) • The scope of Part II of the GMP Guide is described as follows: *These guidelines apply to the manufacture of active substances for medicinal products for both human and veterinary use. (p. 5)* • The scope of ICH Q7 is described as follows: *This Guide applies to the manufacture of APIs for use in human drug (medicinal) products. (p. 1)* Therefore, the proposed revised Annex 2 creates <u>multiple</u> sets of requirements for manufacture of BDS, by separating these requirements into the three different documents above. Furthermore, we believe the proposed revision creates <u>inconsistent</u> sets of requirements, because the proposed revised Annex 2 appears to be far more restrictive for BDS than the other two documents (please see our comments below for details).	(please also see our comments on Table 1, below). We also suggest the that the requirements for BDS for monoclonal antibodies and therapeutic proteins made using recombinant technology be incorporated back into a revised Part II of the GMP Guide, and that the requirements for BDS used in advanced therapeutic medicinal products be addressed in a new and separate section within Part II of the GMP Guide. Finally, we suggest that the current content and title of Part II of the GMP Guide be revised to cover all APIs and BDS so that Part II of the GMP Guide is consistent with the intent and content of ICH Q7 and does not address "Active Pharmaceutical Ingredients used as Starting Materials" only. The new title of Part II of the GMP Guide could be the same as that of ICH Q7: *"Good Manufacturing Practices for Active Pharmaceutical Ingredients"*
Table 1 page 3	Table 1 in the proposed revised Annex 2 does not seem to be consistent with Table 1 of Part II of the GMP Guide and ICH Q7; because types of manufacture are mixed with types and sources of materials: *i.e.*, fermentation is listed as a type and source of material when it could be listed as a manufacturing type.	We suggest that "manufacturing type" and "source and material type" be separated into two different columns. We also suggest that "classical fermentation" be added as a manufacturing type (please note, this term appears in Table 1 of Part II of the GMP Guide, on p. 7). Additionally (and in alignment with our suggestions regarding "scope" above) all text related to BDS manufacturing should be removed from this table.

PART A page 4	In keeping with our suggestions above, a statement should be added to clarify that PART A requirements do not apply to BDS. Lack of clarity about the applicability of requirements in this section could lead to misinterpretations by industry and/or regulators during inspections.	We suggest that a clarifying statement be added at the beginning or Part A (or alternatively in the "Principle" section which also begins on page 4, for example: *"The requirements in this Annex apply only to the biological medicinal products."*
Part A, #4 page 5	It is not clear from whom "*advice should be sought*" regarding "personnel involved with live and genetically modified organisms." Furthermore, we note that manufacture of BDS using recombinant organisms, particularly E. coli and CHO cells, has been done for almost three decades and is well understood, therefore it is not clear what advice, in most circumstances, would be necessary.	We suggest clarification or removal of this statement.
Part A, #5 page 5	Requiring a "*documented risk assessment*" specifically for BDS manufacturing is not required by ICH Q7 and represents an increase in regulatory burden without providing any additional assurance of patient safety or public health. Furthermore, we note that flow of personnel within a manufacturing facility using recombinant organisms is generally well understood.	We suggest that the final statement in subsection 5 be reworded as follows (addition underlined): "*The restrictions on the movement of all personnel <u>in a biological medicinal product manufacturing facility</u> (including QC, maintenance and cleaning staff) should be controlled on the basis of a documented risk assessment".*
Part A, #6 page 5	Product specific dedication of equipment, as proposed here, does not either "*reduce variability*" or "*enhance the reproducibility*" of BDS manufacturing processes.	We suggest that subsection 6 be deleted or that additional justification for this approach be provided.
Part A, #9 page 6	We are not clear on what is meant by "*utilising the principles in Annexe 1*" in the following statement: *"Where aseptic processes are used (e.g. inoculation), control measures should be put in place following a*	We suggest that the last statement of this subsection be reworded as follows (addition underlined): "*Where aseptic processes are used (e.g. <u>for biological medicinal product manufacturing</u>), control measures*

	documented risk-assessment, utilising the principles in Annexe 1". The burden required to comply with Annex 1 for control measures employed in BDS manufacture would not provide any additional assurance of patient safety or public health.	*should be put in place following a documented risk-assessment, utilising the principles in Annexe 1".*
Part A, #10 page 6	The references to Section 3 (Personnel) and Section 5 (Process Equipment) of Part II of the GMP Guide as further guidance are not specific nor are they accurate. These two Sections of Part II of the GMP Guide do not address risk assessment. Furthermore Part II of the GMP Guide is specific to active substances while subsection 10 of the proposed revised Annex 2, as written, addresses "*biological medicinal product*".	We suggest that the last sentence of subsection #10 be removed.
Part A, #10 and #12 page 6	In both subsections, the requirements for "*documented risk management and documented risk assessment*" place new regulatory burden on manufacturers of monoclonal antibodies and therapeutic proteins made using recombinant technology, without providing additional assurance of patient safety or public health.	We suggest that this requirement be removed, or made specific (with a rationale provided) to particular types of products for which such documentation would be necessary.
Part A, #15 page 6	We are not clear on the requirement that "*air filtration units should be specific to the processing area concerned …*". How broadly is the term "*processing area*" to be interpreted? Is all of cell culture a single "*processing area*"? Is all of purification a "*processing area*"? We suggest that a prohibition on use of recirculating air within, for example, a cell culture suite or a bioreactor suite is not justified by safety data. With respect to manufacture of monoclonal antibodies or therapeutic	We suggest that this requirement be removed, or made specific (with a rationale provided) to particular types of products for which such documentation would be necessary.

	proteins made using recombinant technology, a requirement for single pass air in these types of areas would result in a significant increase in cost (the size of the increase would be based on the size and number of air handlers and fans that would be required) and will require renovation of most existing facilities.	
Part A, #16 page 16	The document indicates that "*decontamination (e.g. by fumigation)*" is to be validated. The choice of disinfectant, cleaning agent or fumigant will depend on the nature and identification of the "contaminant". We note that fumigation could represent an unjustified safety hazard and should be a rare event; therefore it is not a good example. Furthermore, we note that decontamination methods would be difficult to validate prospectively. We do agree that disinfectants or cleaning agents used in decontamination should be supported by appropriate lab scale studies to demonstrate effectiveness of the agents used relative to the specific contaminant, and that decontamination activities should be conducted according to a written procedure or protocol.	We suggest the removal of fumigation as an example. We also request clarification of the regulatory expectations concerning validation of decontamination methods.
Part A, #23 pages 7 - 8	Establishing "*look-back procedures*" and other requirements for flock and herd control is relevant only for situations where the BDS or biological medicinal product is derived directly from animals' blood or tissues. Raw materials that are sourced from animals (e.g. animal serum used in cell culture) should comply with the TSE regulations.	We suggest the removal of this requirement.
Part A, #32	Generally, the manufacturer does not know the	We suggest rewording of subsection 32 as follows:

page 8	identity of the recipient of the medicinal product. We agree that industry should have clear documentation of "*batch*" or "*lot*", and participate with other stakeholders in the establishment of systems for traceability throughout the distribution chain.	"*A clear definition of what materials constitute a 'batch' or 'lot' and a system for traceability of all manufacturing related information shall exist".*
Part A, #36 page 9	We are concerned about the statement requiring "*the preparation of solutions and buffers should comply with the requirements of Annex 1*". If this is meant to refer to all solutions and buffers used in manufacture of BDS for monoclonal antibodies and therapeutic proteins made using recombinant technology, it is represents a burden and cost that does not provide additional assurance of patient safety or public health. Additionally, the statement "*Given that the risk and consequences of contamination to the product is the same irrespective of the stage of manufacture*" is of particular concern when referring to manufacturing operations performed under well established GMP principles, and is also inconsistent with the principles from ICH Q9.	We suggest the removal of subsection 36.
Part A, #45 page 10	"*Edge of failure*" testing is fit for research/development and design space, but not for validation or for use during daily operations. Performance and operational parameters must be established based on sound validation studies and should not include evaluations at the edge of failure.	We suggest rewording of subsection 45 as follows: *"Critical process steps, process conditions or other input parameters which affect product safety and / or efficacy, must be identified, documented and validated".*
Part A, #46 pages 10 - 11	The requirement for reconciliation of articles entering and leaving rooms during manufacture of BDS provides no additional assurance of patient safety or public health.	We suggest rewording of subsection 46 as follows (addition underlined): "*Articles and materials, including documentation, entering a <u>biological medicinal product</u> production*

		room should be carefully controlled to ensure that only articles and materials concerned with production are introduced. There should be a system <u>that</u> ensures that articles and materials entering a room are reconciled with those leaving so that their accumulation within the room does not occur."
Part A, #47 page 11	The requirements in this subsection should not apply to articles and materials entering and leaving rooms during manufacture of BDS. They provide no additional assurance of patient safety or public health.	We suggest rewording the first sentence of subsection 47 as follows (addition underlined): "*Heat stable articles and materials entering a <u>biological medicinal product manufacturing</u> clean area or clean/contained area should do so through a double-ended autoclave or oven."*
Part A, #56 pages 11 - 12	The requirements to transfer the mixture to a second sterile vessel or to invert and shake the contents of the original vessel are not justified for manufacture of monoclonal antibodies and therapeutic proteins made using recombinant technology. They are unnecessarily restrictive and represent a regulatory burden that is not justified by providing additional assurance of patient safety or public health. Current facilities for manufacture of monoclonal antibodies and therapeutic proteins made using recombinant technology do not generally have this capability.	We suggest removal of subsection 56.
Part A, #59 page 12	We agree that in general chromatography resins should be dedicated to a single product. Large chromatography column housings, with appropriate validated cleaning, should be acceptable for multi-product use in the purification of monoclonal antibodies and therapeutic proteins made using recombinant technology (while the column parts may be dedicated).	As noted in our comments above, we suggest that requirements for purification of monoclonal antibodies and therapeutic proteins produced using recombinant technology remain in Part II of the GMP Guide and ICH Q7. Requirements for vaccines and advanced therapy medicinal products should be incorporated into revised Part II of the GMP Guide in a new and separate section.

Part B4, #1 and #2 page 14	The principles articulated in subsections 1 and 2 are present throughout Part II of the GMP Guide and ICH Q7 and are not specific to recombinant products only.	We suggest removal of subsections 1 and 2 of Part B4.
Part B4, #3 page 15	Monitoring the stability of the expression construct is already required as part of the maintenance of the master cell bank (MCB) and working cell bank (WCB) by ICH Q7 and Part II of the GMP Guide. Furthermore the maintenance of the MCB/WCB is not included in Table 1 of the proposed revised Annex 2 and therefore it does not appear to be part of the scope of Annex 2.	We suggest removal of subsection 3 of Part B4.
Part B5, #2 page 15	Monitoring the stability of cell / hybridoma lines is already required as part of the maintenance of the MCB/WCB and is covered in detail in Part II of the GMP Guide and ICH Q7. Furthermore the maintenance of the MCB/WCB is not included in Table 1 of the proposed revised Annex 2 and therefore it does not appear to be part of the scope of Annex 2.	We suggest removal of subsection 2 of Part B5.