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15 July 2010

European Commission
Enterprise and Industry Directorate General
Consumer Goods, Pharmaceuticals
B-1049 Brussels
Belgium
BY EMAIL TO adm-gmdp@ema.europa.eu and ENTR-GMP@ec.europa.eu

RE: ENTR/C/8/SF D(2010) 380334: Draft Annex 2, Revision 2: Manufacture of Biological Medicinal Products for Human Use

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the European Commission for the opportunity to submit comments on the "*Annex 2, Revision 2, of the EU GMP Guide: Manufacture of Biological Medicinal Products for Human Use"*.

BIO represents more than 1,200 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, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

As stated in previous BIO comments,[1] we welcome revisions to 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 GMPs for advanced therapy medicinal products (ATMP), such as gene therapy,

[1] BIO comments on "Draft Annex 2: Manufacture of Biological Medicinal Products for Human Use", March 14, 2008, http://bio.org/reg/20080314.pdf

somatic cell therapy medicinal products and tissue engineered products. While the second revision has been significantly improved over the previous draft, we continue to be concerned that the proposed revised Annex 2 creates an inconsistent set of requirements for biological (drug) substance (BDS) manufacture.

GENERAL COMMENTS:

I. *Unclear Relationship between the Revisions and Annex 1, Part 1, and Part 2 of the GMP Guide:*

Annex 2 is stated to be applicable to both Part I and Part II of the GMP Guide. It is unclear, however, to which section the various paragraphs apply. The manufacturer is asked to consider the application of principles in Annex 1 relative to active pharmaceutical ingredient (API) manufacture as well as in media and buffer preparation. Annex 1 is only applied to APIs when they are aseptically manufactured. Other APIs should be made under a control strategy that ensures minimization of bioburden, as described in Part II and therefore, Annex 1 should not be mentioned as relevant for these products. We are concerned that the lack of clarity and overlapping direction will result in differential application of requirements and inconsistent expectations and application by the inspectorate.

II. *Annex 2 should not include Requirements for Monoclonal Antibodies or Recombinant Therapeutic Protein Drug Substances*

Annex 2 addresses only novel Advanced Therapeutic Medicinal Products where Part I and Part II cannot be applied or additional requirements are necessary. Requirements for monoclonal antibodies or recombinant therapeutic protein drug substances are already incorporated in Part II of the GMP Guideline. Annex 2 should not include requirements for monoclonal antibodies or recombinant therapeutic protein drug substances. Please clarify that Annex 1 is only applicable to aseptically manufactured medicinal drug product or aseptically manufactured drug substance.

III. *Multi-Product Facilities are Appropriate for Many Types of Biologic Product:*

It appears that the starting point for manufacturing facilities and equipment is that they should be product dedicated. For specific product categories like sensitizing agents and potent compounds this may be reasonable. Monoclonal antibodies and recombinant therapeutic proteins, however, have been successfully made in multi-product facilities and shared equipment for over a decade. Focus on dedicated facilities and equipment seems unusually regressive for these types of products. Annex 2 should consider and allow for current industry use of valid and widely accepted manufacturing platforms such as multi-product facility design and new regulatory principles of ICH Q8, Q9 and Quality systems as described in ICH Q10.

IV. *Annex 1 is Applicable only to Aseptically Produced Drug Product or Substance*

Annex 1 should only be applicable to aseptically produced drug product or to aseptically produced drug substance. Annex 1 should not be mentioned as applicable to most APIs and drug substances or preparation of buffers and media components used in their manufacture. Differential application of Annex 1 by the various inspectorate will lead to confusion within the inspectorate and industry.

V. *Specific ICH Recommendations Should be Cross-Referenced:*

In many instances, some of which are identified in the tabulation below, requirements from ICH documents are incorporated into Annex 2. Rather than cutting and pasting text or requirements, we recommend that EMA state that specific ICH guidance should be considered relative to topics such as "Seed lot and cell bank system." Further, moving text from ICH guidance into this annex appears to be increasing the regulatory hurdles and burden in the absence of a demonstration that this will provide additional assurance of public health and safety.

VI. *Revisions Are Worded as Advice, Rather than GMP Requirements:*

The wording of the draft more accurately reflects that of a scientific advice document (*i.e.* Eudralex Vol. 3), not an Annex to the GMP Guideline (*i.e.* Eudralex Vol. 4).

For example:

a. Many times the reader is asked to "consider" possible solutions rather than the Annex simply specifying the requirement or expectation.
b. Possible solutions are provided rather than the expected end result. The GMP Guideline is not an appropriate vehicle to suggest options to industry

CONCLUSION:

BIO appreciates this opportunity to comment on "*Annex 2, Revision 2, of the EU GMP Guide: Manufacture of Biological Medicinal Products for Human Use".*
We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely

/S/

Andrew J. Emmett, MPH
Director for Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
INTRODUCTION		
Scope (p.2-3)	The text indicates that the table is "illustrative only and not meant to describe the precise scope." As such, the table can result in confusion and misunderstanding.	The tabulated requirement to comply with GMP Guidelines and Annexes should not conflict with existing ICH guidance, to which the EMA has previously agreed and approved. Table 1 herein should be harmonized to be in agreement with Table 1 of Part II in the EU GMP Guide or deleted if the table is not meant to identify the scope of this annex.
PART A: GENERAL GUIDANCE		
Premises and Equipment (p.5-7)		
#6 (p.5-6)	Paragraph 6 indicates that principles and guidance in Annex 1 should be taken into account when open operations are conducted as part of drug substance manufacture. We suggest that the application of Annex 1 to early stages of drug substance manufacture are entirely inappropriate. We are concerned about the variable application of these concepts by the different inspectorate.	Please delete reference to Annex 1 in this paragraph.
#8 (p.6)	Paragraph 8 states that "…dedicated production areas should be used for handling of live cells and organisms…" We assume that the "e.g." which identifies ATMP and vaccine production are those items to which	Please state that dedicated production areas should be used for handling of live cells and organisms which are pathogenic or are used in vaccine manufacture.

	this is applicable. We ask for clarification of the "e.g." item.	
#9 (p.6)	Section 9 identifies considerations for the operation of a multi-product facility. This addresses a broad range of issues including spore forming organisms. It is not reasonable nor necessary to address all of the suggestions, a-f, for all product types	Please delete a-f, or specify the product types to which they are relevant. Specify that multi-product facilities must address potential cross contamination and product carryover in a manner appropriate to the product types manufactured in the facility. How this is managed should be determined and justified by the company.
#9d (p.6)	Item 9d suggests that environmental monitoring specific for the production organism be performed in adjacent areas during manufacture and after completion of cleaning and decontamination. This is unnecessarily burdensome and represents an increase in requirements for manufacture of recombinant therapeutic proteins and monoclonal antibodies.	Please delete this requirement or specify the ATMP product types to which this must be applied.
#16 (p.7)	Item 16 indicates that primary containment should be periodically tested to demonstrate absence of leakage. It is not clear what is meant by this statement. Does it mean container closure integrity?	Primary container closure integrity must be established and repeated as necessary driven by manufacturing changes or changes in material components.
#19 (p.7)	Item 19 does not address GMP issues, but rather environmental health and safety concerns.	Please delete this section or simply state that local regulations must be complied with relative to discharge of any effluent.

Documentation (p.9)		
#27 (p.9)	Item 27 requires additional information as part of specifications for biological starting materials. This information should generally not be part of the specification for the material. The suggested items are more appropriately part of vendor qualification and oversight rather than a component of product specification.	The additional information suggested in this item might best be addressed by incorporation into Chapter 7, or section 11 of Chapter 4.
Starting Materials (p.9-11)		
#33 (p.9-10)	Item 33 indicates that starting materials may be used at risk when their testing takes "a long time". This is in conflict with paragraph 31 of Chapter 5 of the EU GMP Guide Part I which states that "Only starting materials which have been released by the Quality Control Department and which are within their shelf life should be used."	Please revise to ensure that no conflict exists between these two items in the GMP Guide and that items are to be released by the Quality unit prior to introduction into manufacture.
Operating Principles (p.12-14)		
#60 (p.13)	Item 60 indicates that "…consideration should be given to contact of all product-contact surfaces exposed to live culture and the transfer to a second vessel." This requirement for transfer to a second vessel appears to originate from an older requirement for treatment of plasma and	Please indicate the product types to which transfer to a second vessel is appropriate. This should not include manufacture of recombinant protein therapeutics and monoclonal antibodies.

	blood product pools. It is not common practice among companies that manufacture recombinant protein therapeutics and monoclonal antibodies.	
#61 (p.13-14)	Item 61 suggests consideration be given to dedication of chromatography equipment to the purification of one product. We certainly agree that resins should be dedicated to a single product. Any expectation that chromatography equipment as a whole is product dedicated is in conflict with general industry practice and is not scientifically supported.	Please remove the statement about considering dedication of chromatography equipment.
Quality Control (p.14-15)		
#69 (p.14)	Item 69 suggests that in process control testing include virus removal and residual DNA content. In general, these items are the subject of validation to ensure their removal and thus lot by lot testing is unnecessary.	Please remove the "(e.g. virus removal, residual DNA content)" from item 69.
#70 (p.14)	Item 70 suggests consideration be given to conducting stability studies using drug product that includes materials made with intermediates at their maximum hold times. This will result in a large burden to industry with no apparent increase in drug safety or efficacy. Further, due to the number and	Please delete section 70 or identify the specific ATMP for which this will provide additional benefit relative to safety and efficacy.

	scale of manufacturing changes these will need to be re-done continually, again with no clear benefit to drug safety and efficacy.	