



Connecting People, Science and Regulation®

PDA Europe gGmbH  
Georg Roessling, PhD  
Sr. Vice President

Adalbertstr. 9  
16548 Glienicke/ Berlin  
Germany

Tel: +49 (0) 33056 2377-0  
Fax: +49 (0)33056 2377-77  
Email: roessling@pda.org  
www.pda.org

#### OFFICERS

Chair:  
Maik Jornitz  
Sartorius Stedim Biotech

Chair-Elect:  
Anders Vinther, PhD  
Genentech

Secretary:  
Rebecca Devine, PhD  
Regulatory Consultant

Treasurer:  
Harold Baseman  
ValSource

Immediate Past Chair:  
John Shabushnig, PhD  
Pfizer

President:  
Richard M. Johnson

#### DIRECTORS

Véronique Davoust, PhD  
Pfizer

Gabriele Gori  
Novartis Vaccines and Diagnostics

Lothar Hartmann, PhD  
F. Hoffman-La Roche

Zena Kaufman  
Abbott

Steven Mendivil  
Amgen

Michael Sadowski  
Baxter Healthcare

Junko Sasaki  
Sumitomo Pharmaceuticals

Amy Scott-Billman  
GlaxoSmithKline

Lisa Skeens  
Baxter Healthcare Corporation

Christopher Smalley, PhD  
Pfizer

Laura Thoma, PharmD  
University of Tennessee

Martin VanTrieste  
Amgen

19 July 2010

European Medicines Agency  
Compliance and Inspection, London  
[ADM-GMP@ema.europa.eu](mailto:ADM-GMP@ema.europa.eu)

European Commission  
Pharmaceuticals Unit, Brussels  
[entr-gmp@ec.europa.eu](mailto:entr-gmp@ec.europa.eu)

#### Reference:

Eudralex, Volume 4, Good Manufacturing Practice  
Draft GMP Annex 2  
Manufacture of Biological Medicinal Substances and Products for Human Use  
ENTR/C/8/SF D(2010) 380334, 09 April 2010

To: Responsible Person: European Commission  
Responsible Person: European Medicines Agency

PDA is pleased to provide comments on the latest revision of EU GMP Annex 2. Our comments were prepared by an expert committee of members with practical expertise in the manufacture of a variety of biological products. We have attached a table in the EMA format that lists both our general and specific comments. These comments augment our 2008 comments on the previous revision of Annex 2.

The revised draft reads well and is very different in approach than previous GMP guidances. We note that efforts have been made to apply not only PDA's technical recommendations on the first draft, but also to include the overall spirit and approaches we recommended. As such the draft provides more flexibility by suggesting risk based approaches and risk rationale for each facility/company and circumstance.

We have concerns about the following issues that will affect the utility and implementation of Annex 2.

**Exclusion of Monoclonal Antibody & Recombinant Therapeutic Protein Products from the Scope of Annex 2:** Consistent with our 2008 comments, we suggest that current Part II of the GMP Guide, aligned with ICH Q7, remains the reference GMP guidance for the manufacture of the drug substance (i.e. API) for classical, well characterized, cell culture/fermentation based biological products such as monoclonal antibodies and recombinant therapeutic proteins. Current GMP Part I adequately addresses sterile drug substance and sterile drug product requirements for such products. As such, we recommend that those classes of products be excluded the Annex 2. Doing this will have the benefit of reducing confusion on the part of industry and inspectorates by avoiding an additional, unnecessary GMP guidance document for such products.

**Dedicated Facilities:** The requirements for dedicated facilities, implied or stated, are inconsistent with modern technology and practices which can, with the use of risk based approaches, modern containment engineering, single-use systems, and comprehensive decontamination/cleaning practices, enable multi-product manufacturing in many organizations. Many products have been successfully produced in multi-product facilities and shared equipment for decades. In addition, dedicated equipment does not necessarily reduce variability or enhance the reproducibility of active substance manufacturing processes. Finally, most products in development rely on multi-product facilities for the manufacture of clinical material.

Again, we appreciate the opportunity to support the development of high quality GMP guidance. PDA is ready to provide support for any activities or discussions that are helpful in furthering the usefulness of revised Annex 2.

With very best regards,

A handwritten signature in black ink, appearing to read "Georg Roessling". The signature is fluid and cursive, with the first name "Georg" being more prominent than the last name "Roessling".

Georg Roessling, Ph.D.  
Senior VP, PDA Europe  
[Roessling@pda.org](mailto:Roessling@pda.org)

cc: J. Lyda, R. Levy, R. Dana, S. Roenninger

Attachment



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

19 July 2010

Submission of comments on:

EudraLex, Volume 4  
EU Guidelines for Good Manufacturing Practice  
Medicinal Products for Human and Veterinary Use

GMP Annex 2  
Manufacture of Biological Medicinal Substances  
and Products for Human Use  
Draft

Brussels, 09 April 2010  
ENTR/C/8/SF D(2010) 380334

**Comments from:**

**Parenteral Drug Association (PDA), Berlin**

**Contact: James C. Lyda, [lyda@pda.org](mailto:lyda@pda.org)**

*Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.*

*When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).*



## 1. General comments

PD A #	Stakeholder number	General comment (if any)	Outcome (if applicable)
1		<p><b>Comment 1: Positive Aspects of the Revised Draft:</b> The document reads well and is very different in approach than previous GMP guidances. We note that efforts have been made to apply not only PDA's technical recommendations on the first draft, but also to include the overall spirit and approaches we recommended. As such the draft provides more flexibility by suggesting risk based approaches and risk rationale for each facility/company and circumstance.</p>	
2		<p><b>Comment 2: Exclusion of Monoclonal Antibody &amp; Recombinant Therapeutic Protein Products from the Scope of Annex 2:</b> Consistent with our 2008 comments, we suggest that current Part II of the GMP Guide, aligned with ICH Q7, remains the reference GMP guidance for the manufacture of the drug substance (i.e. API) for classical, well characterized, cell culture/fermentation based biological products such as <u>monoclonal antibodies and recombinant therapeutic proteins</u>. Current GMP Part I adequately addresses sterile drug substance and sterile drug product requirements for such products. As such, we recommend that those classes of products be excluded the Annex 2. Doing this will have the benefit of reducing confusion on the part of industry and inspectorates by avoiding an additional, unnecessary GMP guidance document for such products.</p>	
3		<p><b>Comment 3: Dedicated Facilities:</b> The requirements for dedicated facilities, implied or stated, are inconsistent with modern technology and practices which can, with the use of risk based approaches, modern containment engineering, single-use systems, and comprehensive decontamination/cleaning practices, enable multi-product manufacturing in many organizations. Many products have been successfully produced in multi-product facilities and shared equipment for decades. In addition, dedicated equipment does not necessarily reduce variability or enhance the reproducibility of active substance manufacturing processes. Finally, most products in development rely on multi- product facilities for the manufacture of clinical material.</p>	

## 2. Specific comments on text

PDA No.	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
4	Pg 2 Scope		<p>Comment and rationale: See General Comment 2, and explanatory notes at end of this table. PDA recommends that monoclonal antibody and recombinant therapeutic protein products be exempted from the scope of Annex 2 (those products being adequately covered by GMP Part 1 and Part 2.)</p> <p>Proposed change (if any): Please add the following paragraph to the scope of Annex 2: <b>“Classical well characterized Biotechnology cell culture/fermentation products (such as monoclonal antibodies and recombinant therapeutic protein products) are excluded from the scope of this annex and the GMP Part I and Part II adequately addresses manufacturing requirements for these product types”</b></p>	
5	Pg 3 Scope & Table 1 Row 3		<p>Comment and rationale: Consistent with the preceding comment, the terms “Biotechnology” “Recombinant”, and “Mab” should not appear Row 3 of Table 1. In addition, this row indicates that the preparation of the MCB and WCB is within the scope of the Annex. In Part II of the EU GMP Guide, such activities are not governed under explicit GMP requirements, although maintenance of the working cell bank is covered under GMP requirements for API manufacture. Thus, this table appears to impose new requirements for API “Biotechnology – fermentation/cell culture” manufacture beyond existing GMP expectations. We note the text in the Scope (pg2) indicates that the Table 1 is “illustrative only and not meant to describe the precise scope.” As such, the table seems unnecessary and can result in confusion and misunderstanding among both industry and the inspectorates.</p> <p>Proposed change (if any): To resolve the above issues, we recommend deletion of Row 3, “Biotechnology – fermentation/cell culture” from Table 1.</p>	

PDA No.	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
6	Pg 5 Part A. General Guidance: Personnel, Para 3		<p>Comment and rationale: The last sentence makes a blanket statement regarding live organisms and GMOs that could affect the health status of personnel. There are many live vaccines and GMOs that are non-pathogenic with the risk to personnel much reduced. Some consideration of these organisms needs to be made to avoid unnecessarily restrictive requirements for non-pathogenic organisms.</p> <p>Proposed change (if any): Replace the last sentence with the following paragraph. <b>"For live or genetically modified organisms, health monitoring should be commensurate with the risk. For example, where organisms that are non-pathogenic and are subject to biological containment level 1 and 2 requirements, the risks are much reduced".</b></p>	
7	Pg 5 Part A. General Guidance: Personnel, Para 4		<p>Comment and rationale: Para 4 implies that staff in a multi-product facility would only be able to work in one (1) area dedicated to one (1) product on a daily basis. This type of segregation is unnecessarily restrictive for most facilities with appropriate change over procedures in place. Often, several bioreactors or fermentors are in operation simultaneously in one facility and one room. Second and third sentence are too prescriptive regarding movement of personnel.</p> <p>Proposed change (if any): Delete 2nd and 3rd sentences, and replace with: <b>"Restrictions on the staff access to multiple product areas should be considered with certain agents where the consequences of possible cross contamination have a critical impact on patient safety."</b></p>	
8	Pg 6 Part A. General Guidance:		<p>Comment and rationale: Paragraph 6 (last sentence) indicates that principles and guidance in EU GMP Annex 1 should be taken into account when open operations are conducted as part of drug substance manufacture.</p>	

PDA No.	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
	Premises and Equipment, Para 6		<p>The principles of GMP Annex 1 are frequently not applied by inspectors appropriately and consistently, and the use of Annex 1 is becoming a defacto requirement during inspections. Also, the application of Annex 1 to early stages of non-sterile drug substance manufacture is inappropriate. We are concerned about the variable application of these concepts by the different inspectorates.</p> <p>Proposed change (if any):  <b>Delete final sentence of this paragraph referencing Annex 1.</b></p>	
9	Page 7 Part A Premises & Equipment Para 17		<p>Comment and rationale:  The proposed text uses “sterilization in place” as a general term. The generally accepted term industrial usage is “steam in place” where sterilization in place is one of the selected outcomes</p> <p>Proposed change (if any):  <b>Change “sterilization in place” to “steam in place” and inside the parenthesis change “steam in place” for “sterilization in place”</b></p>	
10	Page 13 Part A Operating Principles Para 61		<p>Comment and rationale:  Third sentence (“Consideration should be given...”) implies that chromatography columns should be product-specific. While chromatography resins may be dedicated, it is not general practice for housings to be dedicated.</p> <p>Proposed change (if any):  For clarity, revise the statement to read, “Consideration should be given ... to dedicate chromatography <del>resins equipment</del> to the...”</p>	
11	Pg 14 Part A Quality Control		<p>Comment and rationale:  Biotech cell culture processes for some products may consist of 6-10 protein purification steps. For</p>	

PDA No.	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
	Para 70		<p>every step typically a few hours hold time are assigned to address batch to batch variations in processing time. The paragraph may suggest that all assigned hold times should be specifically accumulated and the resulting final product put on stability. This is reasonable only for steps where the intermediate can be stored for an extended period of time (days to weeks).</p> <p>Proposed change (if any):</p> <p>Where <del>in-process hold steps exist</del> <b>intermediates can be stored for an extended period of time, e.g. days to weeks</b>, considerations should be given .....</p>	
12	Pg 18 Part B		<p>Comment and rationale: See General Comment 2, and explanatory notes at end of this table. PDA recommends that monoclonal antibody and recombinant therapeutic protein products be exempted from the scope of Annex 2 (those products being adequately covered by GMP Part 1 and Part 2).</p> <p>Proposed change (if any): <b>Delete from Part B, section B5 "Recombinant Products."</b></p>	
13	Pg 18 Part B		<p>Comment and rationale: See General Comment 2. PDA recommends that monoclonal antibody and recombinant therapeutic protein products be excluded from the scope of Annex 2, as those products are adequately covered by EU GMP Part I and Part II.</p> <p>Proposed change (if any): <b>Delete from Part B, section B6 "Monoclonal Antibody Products."</b></p>	
14	Page 21 Part B		<p>Comment and rationale: The proposed text for viral gene therapy products is absolute ["...in the same area is not</p>	

PDA No.	Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
	Gene therapy products Para 9		<p>acceptable"] and does not reflect the Quality Risk Management principles listed in earlier paragraphs. The previous paragraph states that "closed systems should be used wherever possible". Some process steps may be combined with engineering controls to eliminate risk of cross contamination. If the process runs in a closed system then concurrent production of different viral gene therapy vectors could be acceptable based on Quality Risk Management principles.</p> <p>Proposed change -revised text: Delete entire first sentence of this para, and replace with new sentence below. Final para 9 will read as: <b>Concurrent manufacture of different gene therapy vectors (viral or non-viral) in the same area should be controlled on the basis of quality risk management principles to avoid cross contamination.</b> Changeover procedures between campaigns should be demonstrated to be effective.</p>	
15	Pg 24 Glossary Hybridoma		<p>Comment and Rationale: Definition for 'hybridoma' is revised for clarity.</p> <p>Proposed change: Change definition to, "An immortalised cell line <b>that secrete desired (monoclonal) antibodies and are</b> typically derived by fusing B-lymphocytes with a tumour cell. <del>that secrete desired (monoclonal) antibodies."</del></p>	
End of Comments				