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Reference:
Eudralex, Volume 4, Good Manufacturing Practice
Draft Annex 2
Manufacture of Biological Medicinal Product for Human Use
(Brussels, 03 September 2007/rev.)
Consultation deadline: 14 March 2008

To: Responsible Person(s): European Commission
Responsible Person(s): EMEA

PDA is pleased to provide comments on the revision of EU GMP Annex 2. Our comments were prepared by an expert committee of members with practical experience in the manufacture of a variety of biological products. We have attached a table that lists both our general and specific comments. The PDA committee consisted primarily of established manufacturing companies, large and small. Research organisations and academia were not contributors. For this reason, PDA did not address in detail sections of the guidance relating to advanced therapies.

We have concerns about the following issues that will affect the utility and industry/user acceptance of draft Annex 2.

Establishing a Clear Scope
The stated Scope of draft Annex 2 parallels and sometimes is inconsistent with the GMP guidance for active substances (APIs) already defined in EU GMP Part II (based on the ICH Q7 standard). As such, GMP guidance for active substances and biological medicinal products can be found in several sources including GMP Part I (which includes Annex 2) and GMP Part II. The guidance in draft Annex 2 appears to be more prescriptive for active substance manufacturing than existing GMP Part II.

We offer the following scope clarification for your consideration:

a. **Current EU GMP Part II** should remain the reference GMP guidance standard for the vast majority of active substances (APIs) for marketed products, including those using well-established cell culture/fermentation processes, e.g., monoclonal antibodies and therapeutic products.
b. **Revised GMP Annex 2** should, to the extent possible, address GMP guidance for the manufacture of biological medicinal products, as its title suggests. The Annex should address special processes or products where current GMP guidance is not adequate, e.g. advanced therapy products, certain vaccines, and other novel therapeutic biological medicinal products.

Innovation and operational controls
The annex appears ambivalent regarding innovation and the evolving international guidance on pharmaceutical manufacturing and quality, e.g., Quality by Design (QbD), PAT, and ICH Q8, Q9 and Q10. We recommend the Annex clearly state that innovation is welcome to support GMP compliance, and that GMP for biological medicinal products should be interpreted in the environment of the evolving ICH Q8, Q9, and Q10 efforts. These statements could appear in the Explanatory Notes and Scope.

Non-GMP Guidance
GMP Part I and Part II clearly state that they do not cover safety aspects for the personnel engaged in manufacturing, nor do they address protection of the environment. There are adequate local and national legislation applicable to these valid needs. We suggest that, to the extent possible, reference to these issues be removed from the revised annex.

There are many types of biological medicinal products on the market, or under development, and each varies in the level of hazard from transmissible biological agents. The draft annex should embrace a risk-based approach to identify and control transmissible biological agents, at all stages in manufacture, based on the product, manufacturing processes and applied technology. Generally, information required in the registration filing, including TSE control, should not be separate from GMP guidance.

Insights from Annex 2 Open Meeting, 19 February 2008, Budapest
During the open meeting, there was a consensus that the industry may be perceived as 'over interpreting' the wording of the Annex, e.g. use of dedicated facilities and equipment, and the application of Annex 1 for active substances. We recognize that the text of Annex 2 does suggest that manufacturers have some discretion regarding the GMP requirement for such issues. The most common reason for this 'over interpretation' voiced at the open meeting is the belief, by those subject to inspection by Member State Inspectorates, that manufacturers will usually be held to the highest GMP standard inferred from the guidance text. As a result, those inspected will routinely have to justify the decision to not adopt that "highest standard," even if it is qualified in the Annex as 'where appropriate', 'should be considered', etc. We believe this issue must be addressed by all parties through open communication, training, and the building of consensus among stakeholders regarding interpretation of the text. PDA would be willing to facilitate further open discussion through workshops and other training venues.

Again, we extend our appreciation for the opportunity to support the development of high quality GMP guidance. PDA is ready to give support for any activities or discussions that are helpful in furthering the usefulness of revised Annex 2. Our contact for this issue is James C. Lyda, lyda@pda.org, +41 61 701 9550.

With very best regards,

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cc: J. Lyda, R. Levy, R. Dana, Z. Kaufman

Attachment

PDA Comments to EMEA
Eudralex, Volume 4
Good Manufacturing Practice

Draft Annex 2:
Manufacture of Biological Medicinal Product for Human Use

Brussels, 03 September 2007/rev.
Consultation due date: 14 March 2008

CONTACT: James C. Lyda, Director Reg Affairs, PDA Europe : lyda@pda.org, +41 61 701 9550

NOTE ON PDA COMMENTS FOLLOWING ANNEX 2 OPEN MEETING, 19 FEBRUARY 2008, BUDAPEST:
During the open meeting there was a consensus that the industry may be perceived as 'over interpreting' the wording of the Annex, e.g. use of dedicated facilities and equipment, and the application of Annex 1 for active substances. We recognize that the Annex 2 text allows manufacturers some discretion regarding such issues. The most common reason for this 'over interpretation' voiced at the open meeting is the belief, by those subject to inspection by Member State Inspectorates, that manufacturers will usually be held to the highest GMP standard inferred from the guidance text. As a result, those inspected will have to routinely justify the decision to not adopt that standard, even if it is qualified in the Annex as 'where appropriate', 'should be considered', etc. For example, manufacturers who have operated without dedicated equipment for years are anxious that they may in the future have to routinely justify a manufacturing platform that was designed and successfully used for multi-product production. PDA believes this issue must be addressed by all parties through open communication, training, and the building of consensus among stakeholders regarding interpretation of the text.

GENERAL COMMENTS: PDA welcomes this revision of Annex 2 and appreciates the opportunity to provide technical commentary during the consultation period. We also welcome future GMP guidance for advanced therapy medicinal products (i.e., cell based gene therapy, somatic cell medicinal products, and tissue engineered products). However, PDA has some general concerns about the following issues that will affect the utility and industry/user acceptance of draft Annex 2. Following these general comments are listed our specific comments by page and paragraph.

Scope:
The scope of draft Annex 2 parallels and sometimes is inconsistent with the GMP guidance for active substances (APIs) already defined in **EU GMP Part II** (which is based on the internationally harmonized ICH Q7 standard)**.** As such, GMP guidance for active substances and biological medicinal products can be found in several sources including GMP Part I (which includes Annex 2) and GMP Part II. In our view, draft Annex 2 appears to be more prescriptive for active substances than existing Part II.

We suggest that revised Annex 2, to the extent possible, address only the manufacture of **biological medicinal products**. Guidance for **active substance (API)** manufacture, including classical biologicals and cell culture/fermentation biological products (such as monoclonal antibodies and therapeutic products), is adequately addressed in GMP Part II. In addition, the GMP guidance in Annex 2 should be reserved for advanced therapy products, e.g. new types of products, certain vaccines, and other novel product types, etc., where adequate GMP guidance is not currently established. Annex 2 will be useful focusing on the controls and manufacturing of medicinal products where it is critical to ensure product efficacy and protect patient safety, e.g. medicinal products that cannot be rendered sterile by filtration or other means, and for products that cannot be fully characterised because of their source or elucidation process

We recommend the following scope definitions for your consideration:

a. **Current EU GMP Part II**, aligned with ICH Q7, should remain the reference GMP guidance standard for the vast majority of active substances (APIs) for marketed products, including those using well-established cell culture/fermentation processes, e.g., monoclonal antibodies and therapeutic products.

b. **Revised GMP Annex 2** should, to the extent possible, address GMP guidance for the manufacture of biological medicinal products, as its title suggests. The Annex should address special processes or products where current GMP guidance is not adequate, e.g. advanced therapy products, certain vaccines, and other novel therapeutic biological medicinal products.

Innovation and operational controls:
Draft Annex 2 appears to be ambivalent regarding innovation and the evolving international guidance on pharmaceutical manufacturing and quality, e.g., Quality by Design (QbD), PAT, and ICH Q8, Q9 and Q10. For example, Annex 2 on occasion does require a documented risk assessment to justify decisions. Although this is consistent with ICH Q9, it does not distinguish among the different types of products addressed in Annex 2. It is not necessary to apply the GMP approach used for novel biological products, which have no broad body of GMP experience (e.g. gene therapy), to those products which have several decades of experience as commercially available products (e.g. many vaccines, recombinant DNA products and monoclonal antibodies). Similarly, prevention of contamination associated with live virus vaccines, inactivated virus vaccines or pathogenic organisms may require different controls than those associated with production of monoclonal antibodies or therapeutic products. Such controls would be specialised compared to the controls associated

with products in, for example, *E. coli* or mammalian cell cultures, e.g. CHO cells.

Revised Annex 2 suggests some activities that may not apply to all products, e.g., "*edge of failure*" experiments in the routine process validation, and occasional requirement of a "*documented risk assessment.*" This can lead to confusion in implementation as well as in inspection by regulatory agencies. We propose that ICH Q8, Q9 and Q10 be the standard guidance documents regarding new facilities, new processes, and for improvements to existing operations. In addition, the annex can be interpreted to require processes/systems may need to be validated for early-stage IMP/clinical production. In addition, PDA recommends that references to GMP Annex 1 (sterile medicinal products) as a source of GMP guidance for active substances (e.g. inoculation) be eliminated..

In today's industrial environment, shared equipment and operation of multi-product facilities are common practice for many product types. The suggestion that "*dedicated facilities and equipment should be considered*" represents a step backward in regulatory oversight. Dedicated equipment does not necessarily *reduce variability* or *enhance the reproducibility* of active substance manufacturing processes (as suggested in the revised annex). Multi-purpose and multi-product facilities, using modern cleaning procedures, have an established record of achieving acceptable control of cross-contamination. In addition, most products in development rely on multi- product facilities for the manufacture of clinical material.

Non GMP Guidance

GMP Part I and Part II clearly state that they do not cover safety aspects for the personnel engaged in manufacturing, nor do they address protection of the environment. There already exists adequate local and national legislation applicable to these valid needs. We suggest that, to the extent possible, reference to these issues be removed from the revised annex.

There are many types of biological medicinal products on the market, or under development, and each varies in the level of hazard from transmissible biological agents. The draft annex should embrace a risk-based approach to identify and control transmissible biological agents, at all stages in manufacture, based on the product, manufacturing processes and applied technology. Generally, information required in the registration process, including TSE, should not be addressed in GMP guidance.

Limits of PDA Review:
The PDA review team consisted mostly of established manufacturing companies, large and small. Research organisations and academia were not contributors. For this reason, PDA did not address in detail sections of the guidance relating to advanced therapies.

SPECIFIC COMMENTS -- TEXT OF DRAFT REVISION OF GMP ANNEX 2

Page – Para# Section	Comment and Rationale	Proposed change (if applicable)
Page 1 Title	The title suggests that the annex is specific to biological medicinal products. However, the proposed content also includes aspects related to active substances. The introduction of EU GMP Part II has superseded many aspects of Annex 2 related to biological active substances. See "Scope" in General Comments above.	To align content with title, remove all guidance for active substances from the proposed draft of Annex 2 as these are adequately addressed in GMP Part II.
	Explanatory Note	
Page 1 Explanatory Note	The annex is ambivalent towards the latest international guidance, e.g., QbD, PAT, and ICH Q8, Q9 and Q10. There is also no reference to already existing GMPs for specific product types. See "Innovation and Operational Control" in General Comments above.	We recommend addition of references to ICH Q8, Q9 and Q10, and how they interface with this annex.
Page 1	It will be helpful to add a note on "Non GMP References" with a listing of applicable guidance on the overall approach in satisfying MAA commitments, TSE, and other non GMP references in the Annex	Add note for "Non GMP References"

Page – Para# Section	Comment and Rationale	Proposed change (if applicable)
Page 1 Note 1	Part II of EU GMP covers ALL Drug Substances except whole blood and plasma. This means the API for vaccines, whole blood cells, derivatives/components of whole blood and plasma, gene therapy APIs are all included in GMP Volume 4 Part II. Page 6 EU GMP Part II specifically refers to Annexes 2 -7 where supplementary guidance for certain types of active substance may be found. Annex 2 is frequently inconsistent with Part II. It is important that this is clarified so that products already covered by Part II (API) and other Annexes and Guidelines are not included in Annex 2. This will support the harmonization process and clarity in GMP guidance. See General Comments	Amend explanatory notes to reference Part II.
Page 1 Note 2	The note can be interpreted as duplication of requirements now included in Part II. See General Comments.	Suggest rewording as follows: "The breadth of biological products has increased so, as a result, those products not covered by Part II are addressed in Annex 2"
Page 1 Note 3	Annex 2 will be helpful for new therapies for which GMP guidance is unclear. It is not helpful for well understood, existing products. For clarity, it is helpful to have GMP guidance that applies to specific product or product classes. Part II for API (including biotech API), Annex 4 for immunological products, Annex 7 for herbal, Annex 14 for blood and plasma etc.	Reword note to read: "With new types of biological products for which GMP guidance is needed, Annex 2 applies."
Page 1, Para 4-7	The reference to EU GMP Annex 1 (Manufacture of Sterile Medicinal Products) is inappropriate. GMP Annex 1 and the guidance used for non-sterile API manufacture should be clearly separated. The impact on patient safety is may be different between API and drug product, and therefore different controls apply.	We suggest deleting references to Annex 1 in this note and in other sections of the annex where it is referenced in relation to active substances.

Page – Para# Section	Comment and Rationale	Proposed change (if applicable)
	SCOPE	
Page 2 Scope	The scope should clarify how the annex applies to active substances for use in clinical trials. As GMP Part II contains such guidance, we expect this annex not to apply to active substances for use in clinical trials. As currently written, draft Annex 2 conflicts with sections 19.10 and 19.11 of Part II.	Add statement: "This annex will not normally apply to the manufacture of investigational medicinal products, (IMP) used in clinical trial studies. Please refer to guidance in GMP Part II."
Page 2 Scope 3rd para	See General Comments regarding 'Scope'.	We propose rewording of this paragraph to read: "For many active substances the appropriate GMP guidance is addressed in Part II of the GMP guide. For novel or advance therapy products, where new GMP guidance is necessary, GMP guidance on active substances may be contained in this Annex"
Page 2 Scope 4th para	The reference to Volume 3 is of concern as it is inappropriate to reference MAA aspects into GMP guidance.	We recommend reference to Volume 3 be deleted from this paragraph, which will end after "….(CHMP)."
Page 2 Scope 5th para	As this paragraph does not actually define the scope of the annex, we suggest it should be relocated to the 'Explanatory Note'.	Move this paragraph to the 'Explanatory Note' on page 1.
Page 2 Scope 6th para	Same comment as above. Since this paragraph does not actually define the scope of the annex, it should be relocated to the 'Explanatory Note'. Requirements on TSEs are addressed in Volume 3 and largely covered by registration procedures, thus should not be included in GMP guidance.	Move this paragraph to the 'Explanatory Note' on page 1.

Page – Para# Section	Comment and Rationale	Proposed change (if applicable)
Page 2 Scope 7th para	Local and national laws and regulations apply to the manufacture of genetically modified organisms (GMOs). As the references to the GMO EC Directives do not define the scope of this annex, we recommend they be relocated under 'Explanatory note'.	Move this paragraph to the 'Explanatory Note' on page 1. We recommend shortening the paragraph to read: 'The manufacture and control of genetically modified organisms must comply with local, national and GMP requirements where there should be no conflict.'
Page 3 Table 1	Table 1, which defines the scope of the annex, is inconsistent with aspects of Table 1 in GMP Part II (ICH Q7). For example, under the table in Annex 2, GMP is now applied to additional manufacturing steps, such as establishment of Master Cell Banks and Working Cell Banks. This is also the case for cutting, mixing and/or initial processing of organs and tissues from animal sources. This appears to be an inconsistency between the annex and Part II.	We recommend making the table in Annex 2 consistent with the table in Part II.
	PRINCIPLE	
Page 4 Principle 2nd Para	A new last sentence has been added to this paragraph (compared to existing Annex 2), which states: *"In order to minimise variability (and reduce the opportunity for cross contamination), steps such as dedicating equipment to product, should be considered."* We note that there are proven and reliable cleaning processes to allow for multi-use equipment. This is recognized in Part II, 18.15 and 18.44. The sentence does not account for a risk-based approach. Many Biological products are manufactured in a highly reproducible and consistent manner.	We recommend deletion of the last sentence of this paragraph, i.e. "…In order to minimise variability (and reduce the opportunity for cross contamination), steps such as dedicating equipment to product, should be considered."
	PART A: GENERAL GUIDANCE – PERSONNEL	

Page – Para# Section	Comment and Rationale	Proposed change (if applicable)
Page 4 Personnel Para 1	First sentence: Training requirements vary according to the manufacturing operations. Second sentence: The second sentence gives very specific training guidance, e.g. microbiology, general security, etc. This should be changed to a more general statement depending on the nature of the biological product and the role of the employee.	In the first sentence we recommend replacing "*additional*" with "*appropriate*." This is preferred, as all employees must be appropriately trained according to their job. In the second sentence, reword to read, "Personnel should be given relevant information and technical training to protect personnel and the environment."
Page 4 Personnel Para 2.	The listing of relevant scientific disciplines, e.g. medicine, pharmacy, pharmacology, etc., can be confusing when read literally.	We recommend rewording this paragraph as follows, "Persons responsible for production and quality control should have an adequate background in relevant scientific disciplines and have sufficient practical experience to enable them to exercise their management function for the process in which they are involved. *Or* If the list of disciplines is retained, then change the 'and' to 'or' between the words "immunology" and "veterinary medicine".
Page 5 Para 3.	Some provisions of this paragraph relate to companies working with live virus and vaccine production. For manufacturers of biotech products derived from cell culture techniques or fermentation it is considered too strict. Not all products and not all operations necessitate regular health checks.	At the end of the 2nd sentence after health checks add *where necessary* '"…should be vaccinated where necessary with appropriate specific vaccines and have regular health checks *where necessary*."

Page – Para# Section	Comment and Rationale	Proposed change (if applicable)
Page 5 Para 4	We note the addition of a new sentence at the end of paragraph 4 reading, "*Advice should be sought for personnel involved with live and genetically modified organisms."* It is not clear from whom "*advice should be sought*" and what would be the purpose of such advice. There are almost 3 decades of industrial experience with the manufacture of active substances using recombinant organisms, particularly *E. coli* and CHO cells, and we see no need for special advice for personnel in those industries. We recommend deletion of this sentence due to lack of clarity and the risk of misinterpretation by inspectors and the industry.	We recommend the deletion of the last sentence of this paragraph reading, "…Advice should be sought for personnel involved with live and genetically modified organisms."
Page 5 Para 5	The opening sentence of para 5 states in part*, "In the course of a working day... personnel should not pass from areas where exposure to live organisms... are handled"*. This sentence is an expansion of the sentence in the existing version of Annex 2, adding reference to 'genetically modified organisms, toxins' in the "from" area, and 'dead or inactivated products' in the "to" area. In our view, the statement is general and not applicable to all biologics manufacturing, e.g., MAb production. It seems unrealistic to specify what measures might be used to prevent cross-contamination in the many possible circumstances. Rather, the measures for any particular operation should be based on the actual risk.	We recommend rewording of the sentence as follows: "In the course of a working day... personnel should not pass from areas where exposure to live bacteria or viruses... are handled *unless defined decontamination measures are in place*."

Page – Para# Section	Comment and Rationale	Proposed change (if applicable)
Page 5 Para 6	This paragraph suggests the use of dedicated equipment "to reduce variability and enhance reproducibility." Dedicated equipment, as described here, will not necessarily accomplish either goal. In addition, such an approach may not be feasible for most manufacturers of well defined biotech products, or for many small manufacturers. Please see General Comments regarding "Innovation and Operational Control"	We recommend deletion of this paragraph.
Page 5 Para 7	The degree of environmental control is dependent on factors including the design of the process, the design of the equipment, and the biological safety level. The control program should be assessed using a risk-based approach. If a specific risk has been identified, the environmental monitoring programme should include methods to detect the presence of specific organisms.	We recommend rewording of this paragraph as follows: "The degree of environmental control is dependent on factors including the design of the process, the design of the equipment, and the biological safety level. The control program should be assessed using a risk-based approach. If a specific risk has been identified, the environmental monitoring programme should include methods to detect the presence of specific organisms.
Page 5 Para 8	The need for "advice" addresses Biological Safety Levels, not GMP, so we recommend deletion of this sentence.	We recommend the deletion of the second sentence of this section …"Advice should be obtained…."
Page 6 Para 9	The reference to Annex 1 for GMP guidance on inoculation is inappropriate. We recommend deleting this reference. See General Comments, "Innovation and Operational Control"	We recommend deleting the last phrase of last sentence, "…utilising the principles in Annexe 1." The sentence will end after the reference to "risk-assessment."
Page 6 Para 10	This paragraph suggests the possible use of "…dedicated facilities and equipment," to control the risk of cross-contamination. There are many ways to address control of cross-contamination, including use of validated procedures for	We propose to expand the paragraph to provide for additional methods, as follows: "The risk of cross-contamination between ...may require

Page – Para# Section	Comment and Rationale	Proposed change (if applicable)
	cleaning and sanitizing. Careful planning of the logistics and product flow through the facility and equipment will also reduce this risk. Current practice for recombinant biotech products (e.g. MAb), at many multi-product, licensed facilities in the EU is to control cross-contamination by such measures. We agree that the decision to use or not use dedicated equipment or facilities should be the outcome a documented risk assessment.	additional precautions including, for example, *area decontamination by fumigation, cleaning procedures, control of staff movements,* dedicated facilities and equipment, production on a campaign basis and the use of closed systems."
Page 6 Para 11	We find this paragraph to be ambiguous, but believe it refers to the risk of spreading live organisms by use of equipment, e.g., particle monitoring equipment.	We suggest rewording the paragraph as follows:" "Special considerations are required where there are live organisms or cells in the finished product. Additional controls should be put in place regarding certain equipment that is used in the process. For example, particle monitoring equipment should be dedicated to an area or be designed to enable decontamination".
Page 6 Para 15	The last part of this section could be interpreted to suggest that recirculation of air is not allowed in cell culture areas. Such an interpretation would create a huge burden to manufacturing operations without benefit to product quality.	Reword the section to provide for air handling systems according to the technical requirements and type of organisms involved. 'Air filtration units should be designed and constructed to minimise the risks of cross contamination. For certain types of microorganisms, it might be necessary for air handling units to be specific to a process area and to restrict the recirculation of air.'
Page 7 Para 19	Technical considerations and the nature of the biological process determine the need to prevent leakage, e.g. when hazardous and transmissible agents are used. 'Freedom from the risk of leakage' is ambiguous, and we suggest the clearer statement of 'freedom from leakage' as more appropriate.	Reword to read: "Where necessary, primary containment equipment should be designed and tested to demonstrate adequate control of leakage."

Page – Para# Section	Comment and Rationale	Proposed change (if applicable)
Page 7	***PART A: GENERAL GUIDANCE - Animals***	
Page 7 Para 23	Establishing "*look-back procedures*" and other requirements for flock and herd control are relevant only for situations where the active substance is derived directly from the animal blood or tissues. We propose the removal of this requirement.	Remove the sentence: "A look-back procedure should also be in place for conditions that are not apparent at the time of harvest."
Page 8 Para 28	Interpretation and context of this paragraph require clarification.	Sentence 1: Begin the sentence, "For each animal…." Sentence 2: Reword the sentence, "Specific monographs for certain animal housing and monitoring may apply…"
Page 8 Para 29	This paragraph requires an identification system "to prevent <u>any risk of confusion and to control all possible hazards</u>." (Emphasis added). These are absolute requirements that are impossible to comply with. It is only possible to minimize risk and address identifiable hazards.	Reword the sentence as follows: "…subject of an identification system to minimize risk of confusion and to control identifiable hazards."
Page 8	***PART A: GENERAL GUIDANCE - Documentation***	
Page 8 Para 32	Guidance for defining a batch is already in GMP Part I and Part II. It should be deleted from this annex.	We recommend that all of paragraph 32 be deleted.
Page 9	***PART A: GENENERAL GUIDANCE – Starting Materials***	

Page – Para# Section	Comment and Rationale	Proposed change (if applicable)
Page 9 Para 36	Sentence 4: It is not appropriate to apply Annex 1 to the manufacture of a non-sterile active substance. The consequences of contamination are not the same for an active substance and a biological medicinal product. The risk of contamination should be assessed for all stages of manufacture and then appropriate measures should be implemented. Application of Annex 1 to cell culture, fermentation, and related processes will not benefit patient safety. For these reasons, we believe the final sentence should be deleted.	Delete the last sentence of this paragraph.
Page 9	***PART A: GENERAL GUIDANCE - Seed lot and cell bank system***	
Page 10 Para 41	Sentence 1. There is an editing artefact, and the second part of the sentence, "..it is recommended that records…." was probably intended to be a separate sentence.	Editing correction.
Page 10 Para 43	Sentence 1: To require "identical" treatment of containers during storage is not realistic. Rather, we should apply consistent procedures in the handling and storage of containers. Note that it is common for cell banks to be split into at least two locations as a risk mitigation approach.	Revise sentence 1 to read: "All containers of master or working cell banks and seed lots should be treated consistently during storage according to defined procedures."
Page 10	***PART A: GENERAL GUIDANCE -- Operating principles***	

Page – Para# Section	Comment and Rationale	Proposed change (if applicable)
Page 10 Para 44	Paragraph 44 has been added to revised Annex 2. This is a very general statement that is related more to product and process design (We refer to requirements in Volume 3 for production and quality control of specific product types). The requirement for "monitoring through all production stages…" is absolute and prescriptive. There are many types of biological products and methods to produce them. Approaches such as risk-management, design space, QbD and PAT can be useful to define critical operating parameters and controls to ensure product quality. For these reasons, we recommend this paragraph be deleted.	Delete paragraph 44 from the annex.
Page 10 Para 45	Paragraph 45 has been added to revised Annex 2. As above, the issues described are more appropriately related to product and process design aspects. We recommend a rewording of the paragraph to appropriately reflect GMP guidance.	Reword paragraph 45 as follows: "Critical process steps, process conditions or other input parameters which affect product safety and/or efficacy must be identified, validated, documented and have in-process tests conducted, where appropriate, to verify compliance with requirements."
Page 11 Para 47	Paragraph 47 has been added to revised Annex 2. We understand this guidance to apply when bringing materials into an area where there is an opportunity for product contamination. This guidance appears to be adopted from Annex 1 and is not applicable to many areas and stages in biological manufacture. We recommend rewording the paragraph to account for the risk of contamination.	We recommend rewording of paragraph 47 as follows: "Entry and exit of articles and materials into the production areas should be controlled. The level of control should be appropriate to the risk of contamination to the equipment, processes and manufacturing stage performed in the area. Sanitization, decontamination or sterilization of articles into and out of such areas may be necessary."

Page – Para# Section	Comment and Rationale	Proposed change (if applicable)
Page 11 Para 50	There are many approaches to management of cultures and manufacturing systems including disposable technologies, closed systems, and traditional open systems. We recommend changes to be more generic and allow for new engineering approaches for equipment.	Sentence 1, reword to read: "Addition of materials or cultures to fermenters and other vessels, and any sampling, should be carried out under controlled conditions to prevent contamination."
Page 11 Para 52	During the clinical development phases, verified decontamination measures should be established for the organisms used. The facility should have clearly defined bio-containment procedures in place. We recommend rewording of the paragraph to allow more flexibility.	Reword paragraph 52 to read: "Accidental spillages, especially of live micro-organisms, must be dealt with quickly and safely. Appropriate verified decontamination measures should be available. Scientific data can be used to provide rationales for grouping decontamination procedures for various organisms."
Page 11 Para 53	A proposed revision of the text is offered for ease of understanding and implementation	Reword paragraph 53 as follows: "Decontamination procedures should be applied to removal of paperwork, articles and objects from an area where there is a risk of contamination"
Page 11 Para 54	This statement is redundant and addresses information covered in detail elsewhere. (Refer to Volume 3, 3AB8A, and to the general principles in Part I and Part II. Therefore, we recommend deletion of this paragraph.	Delete paragraph 54.
Page 11 Para 55	This statement is redundant and addresses information covered in detail elsewhere (see immediate preceding comment).	Delete paragraph 55.

Page – Para# Section	Comment and Rationale	Proposed change (if applicable)
Page 12 Para 58	We interpret this paragraph to cover biological medicinal products and active substance intermediates. We suggest to reword the paragraph for clarity.	Reword paragraph 58 as follows: "There should be a system to assure the integrity of closure of containers after filling the final products, or filling of intermediates that represent a special risk."
Page 12 Para 59	We recognize that this statement is in the existing version of Annex 2. However, we believe some revision is necessary during this consultation period. While chromatography resins are usually dedicated, the dedication of columns in a multi-product, cell culture facility is not current practice. Many columns cannot be sterilised. Emphasis should be on bioburden control or sanitisation, not sterility. Nor is it necessary to dedicate chromatography skids as they have validated cleaning procedures. If it can be assured that there is no risk for cross-contamination there is no reason for not using equipment at different stages of another process. Chromatography: it is generally considered sufficient to have the resin dedicated. Cleaning validation assures cleanliness of equipment in general.	A paragraph should be added e.g. stating: "Multi-purpose and multi-product facilities should ensure by verified or validated cleaning and sanitation procedures the cross-contamination between batches and between campaigns are reduced to a defined acceptable level." Reword to: "A variety of product-contact equipment is used for chromatography. In general, chromatography resins should be dedicated to the purification of one product. Chromatography equipment should be appropriately cleaned and sanitised between batches and products. Acceptance criteria, operating conditions, life span and sanitisation or sterilisation method of columns should be defined."

Page – Para# Section	Comment and Rationale	Proposed change (if applicable)
Page 12 Para 61	All aspects of contamination and cross-contamination should be managed not just capping. The approach should be according to the risk of contamination and cross-contamination based on the biological system e.g. live organisms.	Rewording suggested as all the activities in managing contamination of the work environment or must be addressed: "Activities in handling vials containing live biological agents must be performed in such a way to prevent the contamination of other products or egress of the live agents into the work environment of the external environment. This risk assessment should take into consideration the viability of such organisms and their biological classification."
Page 12	***PART A: GENERAL GUIDANCE -- Quality control***	
Page 12 Para 62	We recognize this paragraph is currently in existing Annex 2, but believe the guidance can be revised for clarity. The emphasis should be on the GMP requirements, not on the process controls that are defined and accepted in the Marketing Authorisation Application. Reword the sentence so that it is clear that GMP involves effective implementation of a process that has been properly validated .	Reword paragraph 62 to read: "In-process control testing is performed at appropriate stages of production to control those conditions that are important for the quality of the finished product (e.g. absence of adventitious viruses, residual DNA content)."
Page 13 Para 66	Paragraph 66 is new to the revised Annex 2. The consideration of QC requirements for continuous culture production is no different than the consideration for all manufacturing systems. This perspective applies to all process, and includes a risk assessment to determine the level of in process monitoring to ensure reliable and reproducible quality. As such, we suggest this paragraph can be deleted.	Delete paragraph 66.
Page 13	***B. SPECIFIC GUIDANCE ON SELECTED PRODUCT TYPES***	

Page – Para# Section	Comment and Rationale	Proposed change (if applicable)
Page 13	*B1. ALLERGEN PRODUCTS*	This section should be deleted as it is really a function of the MAA and is Regulatory activity, not specifically GMP.
Page 13	*B2. ANIMAL IMMUNOSERA PRODUCTS*	This section should be deleted as it is really a function of the MAA and is Regulatory activity, not specifically GMP.
Page 13	*B3. VACCINES*	Delete the regulatory relevant topics which are a function of the MAA, not GMP (B3.1, 4, 5, & 7)
Page 14	*B4. RECOMBINANT PRODUCTS* There are well defined Guidelines and GMPs applicable and in place for this class of product. Thus, we recommend these products be deleted from this Annex; or if text remains there should be reference to the following Guidelines and GMPs: Eudralex Volume 3: 3AB1A , 3AB2A etc. Eudralex Volume 4: Part1 & Part II, & Annex 1	Delete section B4, Recombinant Products.
Page 14 B4-1	See comment immediately preceding.	Delete paragraph B4.1.
Page 14 B4-2	These requirements are fully addressed in the Volume 3 guidelines and are a function of the regulatory MAA forming a crucial part of the product design and description not manufacturing GMP	Delete paragraph B4.2 OR Reword as follows: "The capability of the purification process to remove host-cell-derived impurities and process related impurities (e.g. host cell proteins, nucleic acids, carbohydrates, viruses and other impurities) should be assessed using a risk based-approach and should be appropriately validated."

Page – Para# Section	Comment and Rationale	Proposed change (if applicable)
Page 14 B4-3	See preceding comments on B4.1 & 2.	Delete paragraph B4.3.
Page 15	*B5. MONOCLONAL ANTIBODY PRODUCTS*	Delete the regulatory relevant topics which are a function of the MAA, not GMP (B5.1, 2, 3, 4)
Page 14 B5-1	There are well defined Guidelines and GMPs applicable and in place for this class of product. Thus, we recommend these products be deleted from this Annex; or if text remains there should be reference to the following Guidelines and GMPs: Eudralex Volume 3: 3AB1A , 3AB2A etc. Eudralex Volume 4: Part1 & Part II, & Annex 1	Delete section B5.1.
Page 15 B5-2	See comment on B5.1.	Delete section B5-2.
Page 15 B5-3	See comment on B5.1.	Delete section B5.3.
Page 15 B5-4	See comment on B5.1.	Delete section B5.4.

Page – Para# Section	Comment and Rationale	Proposed change (if applicable)
Page 15	*B6. GENE THERAPY PRODUCTS* This is a new class of products. We generally regard the principles of GMP for gene therapy manufacturing to be consistent with those for current licensed biologicals, both vaccines and therapeutic proteins. Some aspects of GMP guidance may be found in GMP Part II. New and special guidance should be included in future revision of Annex 2. The terms and definitions should be consistent with already existing guidance, for example Volume 3, 3AB6A. PDA has not listed substantive comments on this technology as the make up of our review group did not provide the relevant expertise. Our lack of comments should not be regarded as an endorsement of the text in the revised Annex 2.	Not reviewed.
Page 18	*B7. SOMATIC AND XENOGENEIC CELL THERAPY PRODUCTS* PDA has not listed substantive comments on this technology as the make up of our review group did not provide the relevant expertise. Our lack of comments should not be regarded as an endorsement of the text in the revised Annex 2.	Not reviewed.
Page 20	*B8. TRANSGENIC ANIMAL PRODUCTS* PDA has not listed substantive comments on this technology as the make up of our review group did not provide the relevant expertise. Our lack of comments should not be regarded as an endorsement of the text in the revised Annex 2.	Not reviewed.

Page – Para# Section	Comment and Rationale	Proposed change (if applicable)
Page 20	*B9. TRANSGENIC PLANT PRODUCTS* PDA has not listed substantive comments on this technology as the make up of our review group did not provide the relevant expertise. Our lack of comments should not be regarded as an endorsement of the text in the revised Annex 2.	Not reviewed.
Page 21	*B10. TISSUE ENGINEERED PRODUCTS.* PDA has not listed substantive comments on this technology as the make up of our review group did not provide the relevant expertise. Our lack of comments should not be regarded as an endorsement of the text in the revised Annex 2.	Not reviewed.
Page 22	*GLOSSARY*	Not reviewed.

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