PDA Europe

Adalbertstrasse 9
16548 Glienicke/ Berlin
Germany

Tel: + 49 33056 2377-0
Fax: + 49 33056 2377-77
E-mail: info-europe@pda.org
www.pda.org

Glienicke/ Berlin 29 January 2009

David Cockburn
Inspections Sector
European Medicines Agency
7 Westferry Circus
London E14 4HB
United Kingdom
GMP@emea.europa.eu

Sabine Atzor
Pharmaceuticals Unit
Enterprise and Industry DG
European Commission, BREY 10/069
B-1049 Brussels
Belgium
entr-gmp@ec.europa.eu

Ref: EU Guidelines to GMP, Medicinal Products for Human and Veterinary Use, Draft Annex 13, Manufacture of Investigational Medicinal Products (11 April 2008)

Dear David and Sabine:

PDA is pleased to have the opportunity to provide comments on the revisions to Annex 13, GMP for Manufacture of Investigational Medicinal Products. Our comments were prepared by a group of member experts in this field after considerable discussion. Our comments are attached in detail in the requested EMEA format.

In general the proposed revisions are acceptable and helpful. We have proposed some changes in order to allow companies to select their own tools for implementation based on their specific pharmaceutical quality systems. There are two areas where revision of the proposed text is important:

1. Storing reference samples of intermediate product can be problematic and goes beyond generally accepted GMPs for commercial products. This could place a significant new burden on companies. We propose to delete the relevant sentence.

2. The revised annex appears to require the storage of reference samples in the EU except under exceptional circumstances. PDA suggests that the actual location of storage need not be prescribed provided that the sponsor and manufacturer ensure the ability to retrieve and deliver these samples expeditiously if needed. Courier services allow for this to be done from any location in the world within a day or two.

If I can be of further assistance, please feel free to contact me, or our Director of Regulatory Affairs, Jim Lyda at: *lyda@pda.org.*

Yours sincerely,

Georg Roessling, PhD
Senior Vice President
PDA Europe

Cc: Greene, Gambini, Dana, Lyda, Eck

European Medicines Agency

PDA COMMENTS ON
REVISED EU GMP ANNEX 13
MANUFACTURE OF INVESTIGATIONAL MEDICINAL PRODUCTS
(11 April 2008)

COMMENTS FROM PDA Contact: Jim Lyda, lyda@pda.org, +41 79 220 6873

GENERAL COMMENTS

The proposed modifications are generally acceptable. PDA suggests revising some wording in order to clarify the goals to be achieved and to allow each pharmaceutical company to select the appropriate tools for implementation according to their internal quality system

Line no[1]. + paragraph no.	Comment and Rationale	Proposed change (if applicable)	Importance (H/M/L)
Principle	EMEA has additional guidance on IMPs and it might be helpful to users to add a reference to this guidance in the Principle section of Annex 13.	Add reference to: Guidance on Investigational Medicinal Products (IMPs) and Other Medicinal Products Used in Clinical Trials	M
5	For added clarity, and for clearer guidance in emerging markets, we suggest adding an opening statement to this paragraph from the original text of Annex 13 regarding the capability of the cleaning procedure	Add text (in italics) so the paragraph reads as follows : *The cleaning method/procedure should be scientifically sound and capable of cleaning to the predefined limits of residue e.g.* the solubility of the product should be taken into account in decisions relating to selection of the cleaning solvent	M
36 2nd paragraph	Product contained in its primary packaging or finished product covers packaging material, therefore delete redundancy.	Delete in first sentence of this paragraph the words: ~~"packaging material~~"	M
Reference samples	Storing reference samples from intermediate stages goes beyond current GMP requirements for commercial product, and will create a considerable burden for industry. The decision to store or not to store these samples constitutes a business rather than a quality risk.	Delete the 2nd sentence of this paragraph as follows: "~~Where stability permits, reference samples from critical intermediate stages (e.g. those requiring analytical testing and release) or intermediates, that are transported outside of the manufacturer's control, should be kept".~~	H

Public

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 95
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

Line no[1]. + paragraph no.	Comment and Rationale	Proposed change (if applicable)	Importance (H/M/L)
36 4th paragraph	For reasons of clarity and to avoid redundancy delete the phrase "retention samples and blinded product" from this paragraph. Retention samples are addressed in the following paragraph under "Consideration should be given to keeping retention samples…"	Delete the words "and retention" and "including blinded product" to read as shown below: Reference ~~and retention~~ samples of investigational product, ~~including blinded product~~ should be kept for at least two years….."	M
37	The second sentence of the second paragraph of this section suggests that storage of reference samples of finished product in a third country should occur only in exceptional circumstances. Location of storage is less important provided that the sponsor and manufacturer ensure the ability to retrieve and deliver these samples expeditiously if needed. Courier services allow for this to be done from any location in the world within a day or two.	Delete the words "in exceptional circumstances" to read: ~~"In exceptional circumstances~~ The reference samples of the finished product may be stored by the manufacturer in a third country, in which case this should be justified and documented in a technical agreement between the sponsor and that third country manufacturer."	H
44	Suggest deleting the final sentence of this paragraph, which is new text added in the revision. We suggest it is best to leave it to the individual company to establish how best to achieve the objective based on their internal quality system.	Delete last sentence of this paragraph: ~~In practical terms, this can best be achieved through a change control process for the Product Specification File and defined in a Technical Agreement between the QP and the Sponsor.~~	M
Table 2	Directive 91/356/EEC has been superseded by Directive 2003/94	Update as necessary paragraph b)and f)	M

.

These comments and the identity of the sender will be published on the EMEA website unless a specific justified objection was received by EMEA.