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European Commission
Pharmaceuticals Unit
Brussels
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Reference: *Delegated Act on the Principles and Guidelines of Good Manufacturing Practice (GMP) for Active Substances in Medicinal Products for Human Use – Concept Paper submitted for public consultation*
Brussels, 20/01/2012, Sanco.ddg1.d.6(2012)73176
Consultation deadline: 20 April 2012

To: Responsible Person: European Commission
cc: Responsible Person: EMEA Inspections Sector

PDA is pleased to have the opportunity for consultation on this concept paper which proposes an approach to extend the medicinal product GMP to drug substance. Our recommendations were prepared by a group of experts from our worldwide membership with an interest in this issue.

As a preface, we wish to confirm PDA's position on basic foundations of our proposal:

1. We recognize, accept and support the need for robust regulatory action to reduce the risks of falsified medicines and to protect the patients and the pharmaceutical manufacturing community from the threats such medicines represent.
2. However we have an alternate proposal on the final format or outcome of the regulatory process which will provide more clarity for all stakeholders.
3. We make our proposal under the presumption that it can be implemented by the Commission with similar speed as the changes proposed in the concept paper.

Our comments below are structured to answer the five questions in the subject concept paper.

Consultation item No 1:
"…Against this background it is therefore currently envisaged to extend the scope of Directive 2003/94/EC to active substances. Consequently, subject to certain modifications (see below), the provisions of Directive 2003/94/EC would also apply to the manufacturing of active substances."

Q. Do you agree with this appraisal and approach? Please comment.

A. PDA:
We respectfully disagree with this approach and recommend an alternate approach. Medicinal products and active substances can be fundamentally

different in terms of characteristics, formulation and manufacturing processes. As a result, the principles and guidelines for Good Manufacturing Practice (GMP) aspects of medicinal products are frequently very different from active substances. We note that Eudralex Volume 4 has already made the appropriate distinctions between the two in *Part I - Basic Requirements for Medicinal Products*, and *Part II - Basic Requirements for Active Substances used as Starting Materials*.

Our recommendation: We recommend that the existing directive be modified by creation of a new, separate section dedicated to the GMP expectations for drug substance or APIs. The amended directive would then have two separate parts consistent with Eudralex Volume 4: Part I for Medicinal Products (the existing text unaltered), and Part II, for active substances and reflecting Eudralex Vol. 4, Part 2.

Benefit: A clear separation of the GMP rules for drug substance (API) from GMP for medicinal products will reduce the possibility of future unintended consequences resulting from an attempt to combine the two by extending the medicinal product rules to cover API/ drug substance. Having separate statements of guidance for medicinal products and drug substance will benefit the authorities and the industry by mitigating future confusion or gray areas in GMP interpretation and compliance.

Consultation item No 2:
[Regarding the adaptation of Directive 2003/94/EC to active substances….]

Q. Are there other aspects which should be considered? Please comment.

A. PDA:
In the context of our answer to Item No. 1, we have no response on this question.

Consultation item No 3:
Regarding… 2.3. Other provisions on active substances that could be added to Directive 2003/94/EC

Q. Do you consider this list complete? Please comment.

A. PDA:
In the context of our answer to Item No. 1, we have no comments on this question.

Consultation item No 4:
…In particular, an obligation could be placed on the manufacturer of the active substance to ensure that the starting material is sourced from the premises claimed by the manufacturer of the starting material.

Q. Do you agree with this specific point? Do you consider that other provisions specific to active substances should be added?

A. PDA:
In the context of our answer to Item No. 1, we have no comments on this question.

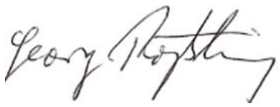
Consultation item No 5:
3.1. Date of transposition of the delegated act

Q. Please comment on section 3. Please raise any other issues or add any other comments you wish to make which have not been addressed in the consultation items set out above.

A. PDA:
If the proposed GMP directive for active substances is written to reflect a quality system consistent with EudraLex Vol. 4 (i.e. the internationally harmonized and implemented ICH Q7 guideline), the implementation date of six months from publication may be appropriate. However, if the directive introduces additional requirements a longer period may be necessary.

Thank you again for the opportunity for PDA members to support the development of practical and effective guidance which can support and protect the public health. Please contact me, or James Lyda of the PDA staff (lyda@pda.org), if you have any questions.

With very best regards,



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