20 October 2011
EMA/CHMP/SWP/598303/2011
Committee for Medicinal Products for Human Use (CHMP)

Concept Paper on the development of toxicological guidance for use in risk identification in the manufacture of different medicinal products in shared facilities

Agreed by Safety Working Party	October 2011
Agreed by GMP/GDP Inspectors Working Group	October 2011
Adoption by CHMP for release for consultation	20 October 2011
End of consultation (deadline for comments)	31 January 2011

Comments should be provided using this template. The completed comments form should be sent to SWP-H@ema.europa.eu

Keywords	***Toxicology, GMP, Dedicated Facilities, Quality Risk Management***

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1. Introduction

A lack of clarity in the existing GMP guide with respect to when a medicinal product should be manufactured in dedicated facilities was identified by the GMP/GDP Inspectors Working Group and led to the publication of a Concept Paper proposing the revision of the relevant sections of the GMP guide (3.6, 5.18 and 5.19) in 2005. It was recommended that Quality Risk Management principles as described in ICH Q9 should be taken into account in the development of any guidance. The GMP/GDP Inspectors Working Group has been working on GMP guidance on various aspects of quality risk management in this context and it became apparent that risk assessment should include, among other parameters, a toxicological evaluation of the products being manufactured in a shared facility. The GMP/GDP Inspectors Working Group recognised that it does not possess all the necessary expertise and therefore referred this aspect to the Safety Working Party.

2. Problem statement

At present there is no defined approach in order to outline a method of deriving acceptable exposure limits for cross contamination between products manufactured using shared facilities. The concern arises that in the absence of any guidance and with a plethora of toxicological tools being available a lack of harmonised interpretation could occur both in pharmaceutical industry and National Competent Authorities. This may result in different production requirements with significant financial impact on manufacturers and potentially, in medicinal products of impaired quality which may adversely affect patients' health

3. Discussion

Currently toxicological data are not always used in establishing limits for cross-contamination. In some cases arbitrary limits such as 1/1000th of the lowest clinical dose or 10ppm are used as limits for cleaning validation. These limits do not take account of the available pharmacological/ toxicological data and possible duration of exposure and may be too restrictive or not restrictive enough. A more scientific approach based on current available pharmacological and toxicological information is required to establish threshold values to be used as part of the overall Quality Risk Management in shared facilities.

The overall objective is for a joint approach to this project by the Safety Working Party and GMP/GDP Inspectors Working Group with respect to revising the relevant parts of the GMP guide and developing clear guidance on appropriate toxicological assessment. Finalisation of guidance on non-toxicological aspects and risk reduction strategies will remain solely with GMP/GDP Inspectors Working Group.

4. Recommendation

The Safety Working Party recommends drafting new guidance on toxicological assessment to be used in the risk identification stage of the Quality Risk Management process in determining whether a medicinal product should be manufactured in dedicated facilities. More specifically the agreed approach should be scientifically based and aim to limit variability in deriving acceptable exposure limits thereby ensuring consistency.

The guidance should be prepared by a drafting group of the Safety Working Party while appropriate input from the GMP/GDP Inspectors Working Group will be taken into consideration. It is expected that

the new guidance will be incorporated as an Annex to the GMP guide supplementing related guidance under development in Chapters 3 and 5 of the Guide.

The drafting group will evaluate all available scientific information related to this topic including data on highly sensitizing materials.

5. Proposed timetable

Concept Paper to be agreed by SWP and GMP/GDP IWG in September 2011.

Concept Paper to be published for a 3 month consultation in October 2011.

1st draft to be discussed at SWP and GMP/GDP IWG in February 2012.

Revised draft to be discussed and agreed by SWP and GMP/GDP IWG in May 2012.

Draft guidance to be published for a 3 month consultation in June 2012.

Final text to be agreed by SWP and GMP/GDP IWG in February 2013.

To be published in March 2013 with a 6 month implementation deadline.

6. Resource requirements for preparation

The development of the guideline will be carried out by the Safety Working Party in co-operation with the Inspectors Working Party.

The Safety Working Party will appoint a drafting group among its members who will prepare an initial guideline. The drafting group will co-ordinate all subsequent activities in the development of the finialised guide including:

- Review internal comments prior to publication for external consultation
- Prepare a new draft for publication
- Review the external comments received after expiration of the external consultation period
- Prepare the overview of comments
- Prepare a new draft for finalisation

The guideline will be discussed at the SWP and the Inspectors Working Group and other meetings as necessary.

7. Impact assessment (anticipated)

As this topic can have a high impact on patient safety and manufacturing costs, harmonised guidance will be beneficial for regulators, industry and social security systems.

8. Interested parties

Drug substance manufacturers, GMP inspectorates and industry associations.

9. References to literature, guidelines, etc.

Concept Paper Dealing With the Need for Updated GMP Guidance Concerning Dedicated Manufacturing Facilities in the Manufacture of Certain Medicinal Products. Published in 2005 (no longer available).