



AD HOC GMP INSPECTION SERVICES GROUP

CONCEPT PAPER ON CHANGES TO CHAPTER 5 OF THE GMP GUIDE

AGREED BY AD HOC GMP INSPECTION SERVICES GROUP	April 2007
DEADLINE FOR COMMENTS	31 August 2007

The proposal will update the existing chapter 5 of the GMP Guide and if possible will be phased in at the same time as existing work being conducted on this chapter as announced in the Concept Paper entitled "Dealing with the need for updated GMP guidance concerning dedicated facilities in the manufacture of certain medicinal products", published in February 2005.

Comments should be provided to GMP@emea.europa.eu
Fax +44 (0)20 7418 8595

KEYWORDS	Qualification, Suppliers, Starting material, Active Substance, Testing, Certificate of Analysis
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1. INTRODUCTION

Chapter 5 of the GMP Guide provides detailed guidance on the production of medicinal products in order to comply with the principles and guidelines laid down in Art. 10 of Directive 2003/94/EC and Directive 91/412/EEC. A concept paper was published in February 2005 to update and clarify GMP recommendations relating to certain products that need to be manufactured in dedicated self-contained facilities in which some change to chapter 5 was envisaged. Additional unrelated needs for work on Chapter 5 have been identified subsequently that may possibly also affect Annex 8 of the GMP Guide (supplementary guidance on sampling of starting materials and packaging materials).

2. PROBLEM STATEMENT

2.1 The obligation for manufacturing authorisation holders to use as starting materials active substances that have been manufactured in accordance with GMP introduced through Art. 46f (50f) of Directive 2001/83(2) is not clearly reflected in the detailed guidelines on GMP. The expectations for the qualification of active substances manufacturers and suppliers should be updated in the light of the new legislation and aligned to other existing guidance (e.g. Guidance on the occasions when it is appropriate for Competent Authorities to conduct inspections at the premises of Manufacturers of Active Substances used as starting materials, Notice to Applicants). Particular consideration should be given to aspects of traceability and confirmation of the origin of active substances.

2.2 While it is understood that the term “starting materials” includes excipients, existing requirements should also be reviewed in the light of the new legal provisions for excipients as defined in Article 46f of Directive 2001/83/EC, as amended, and the resultant GMP Directive for excipients currently under preparation.

2.3 Concerning the testing of starting materials to confirm their suitability for use, it has been established that there are differing practices and expectations of manufacturers by the various National Competent Authorities.

3. DISCUSSION

Although the chapter does provide some guidance on the qualification of suppliers it does not emphasize the obligation to ensure that active substances are produced in accordance with GMP neither is there any guidance as to how this could be achieved. Furthermore the chain of supply for some active substances can be complex and it is felt that guidance should take this into account.

With respect to the testing of starting materials there are two basic approaches. Some Member States require the manufacturer to test starting materials itself while others permit the use of certificates of analysis provided by the supplier. A harmonised approach, taking into account principles of quality risk management, is desirable striking a balance between assurance of quality, and therefore the safety of patients and product efficacy, and the efficient use of resources.

4. RECOMMENDATION

The Ad Hoc GMP Inspection Services group recommends a revision to Chapter 5 of the GMP Guide to address the three points outlined in the problem statement. It specifically considers sections 5.25 and 5.26 as the parts requiring amendment in connection with the obligation to ensure that active substances and certain excipients comply with GMP. It recommended that testing of starting materials be dealt with through a new section inserted after section 5.31 and thus a harmonised approach will be achieved and accepted.

The revised guidance will apply to medicinal products already authorised and on the market, as is normal for amendments to the GMP Guide.

5. PROPOSED TIMETABLE

Release for consultation should be expected by the end of September 2007 with a deadline for comments by the end of March 2008. The expected date for adoption of a final text by the European Commission is October 2008.

6. RESOURCE REQUIREMENTS FOR PREPARATION

Some discussion has already taken place and agreement is expected relatively quickly. A rapporteur has been appointed for each of the two topics covered by this paper. No specific drafting group meetings are anticipated.

7. IMPACT ASSESSMENT

As manufacturing authorisation holders have had a legal obligation since 30 October 2005 to ensure the active substances it uses have been produced in accordance with GMP the development of this guidance will have no resource impact for manufacturers. The guidance is expected to bring together established best practices into the GMP Guide.

The harmonisation of expectations on the testing of starting materials is similarly expected to have no resource impact on manufacturers but should help some manufacturers use existing resources in a more effective way. The revision should bring clarity and transparency into this area of GMP to the benefit of both industry and inspectors.

Any new guidance specifically with respect to excipients will be in response to new legislation. Any resource impact will be taken account of in the related consultation. No additional impact would arise from the guidance itself.

8. INTERESTED PARTIES

No particular need has been foreseen to make provision for interested parties other than through the standard consultation process.

9. REFERENCES TO LITERATURE, GUIDELINES ETC

Directive 2001/83(2)/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to Medicinal Products for Human (Veterinary) Use as amended by Directive 2004/27(8)/EC of the European Parliament and the Council of the 31 March 2004. OJ L-136, 30/04/2004, p.34-57. (OJ L-136, 30/04/2004, p. 58-84).

EUDRALEX Volume 4 - Medicinal Products for Human and Veterinary Use: Good Manufacturing Practice. Chapter 5. European Commission.

Public consultation in preparation of a GMP Directive for Certain Excipients until 30 July 2007:

http://ec.europa.eu/enterprise/pharmaceuticals/index_en.htm

Written Declaration pursuant on pharmaceutical active principles (notably active substances) by the European Parliament dated 04 September 2006 (0061/2006).