EUROPEAN COMMISSION
ENTERPRISE DIRECTORATE-GENERAL

Single market : management & legislation for consumer goods
Pharmaceuticals : regulatory framework and market authorisations

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Ad Hoc GMP Inspections Services Group

Addition to Chapter 6 to the EU Guide to Good Manufacturing Practice

Title: On going Stability

Agreed by ad hoc GMP inspectors services group	October 2003
Released for public consultation	December 2003
Deadline for comments	June 2004
Final draft adopted by ad hoc GMP inspectors services group	
Adopted by Pharmaceutical Committee	
Date for coming into operation	

Note:

The proposed additional text for Chapter 6 of the GMP Guide provides guidance on ongoing stability monitoring thereby clarifying that ongoing stability monitoring is a Community GMP expectation in line with the GMP requirements of our MRA partners.

Proposed addition to chapter 6 of EC GMP Guide

On going stability

6.23 After marketing of a medicinal product, the stability of the product should be monitored according to a continuous programme that will permit the detection of any stability issue (e.g. level of impurities, dissolution profile etc.) associated with the formulation in the package concerned.

6.24 The purpose of the on going stability programme is to monitor the product over its shelf life and to determine whether the product can be expected to remain within specifications under the labelled storage conditions.

6.25 This mainly applies to the medicinal product in the package in which it is sold, but consideration should also be given to the inclusion of bulk product. For example, when the bulk is stored for a certain time before being packaged, the impact on the stability of the packaged product during its shelf life should be studied. If relevant, the stability of reconstituted product can also be monitored.

6.26 The ongoing stability programme should be described in a written protocol, implemented for each marketed medicinal product and formalised as a report, both following the general rules of annex 15. (See also 6.29 below).

6.27 The protocol for an ongoing stability programme should extend to the end of the shelf life period and should include, but not be limited to, the following parameters;

- number of batch(es) per strength and different batch sizes, if applicable
- relevant physical, chemical, microbiological and biological test methods
- acceptance criteria
- reference to test methods
- description of the container closure system(s)
- testing intervals (time points)
- description of the conditions of storage (standardised conditions should be used, i.e. ICH conditions for long term testing, unless otherwise justified)
- any relevant detail regarding handling of the sample between the time it is retrieved from the stability chamber and the time it is analysed
- other applicable parameters specific to the medicinal product.

6.28 Any differences between the protocol for the continuing stability programme and the protocol for the initial stability studies, as submitted in the marketing authorisation dossier, should be justified.

6.29 The number of batches and frequency of testing should provide a sufficient amount of data to allow for trend analysis. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type, if relevant, should be added to the stability programme (unless none is produced that year). The principle of bracketing and matrixing designs may be applied if scientifically justified.

6.30 Worst case situations should be covered within the ongoing stability programme. For example, ongoing stability studies should be conducted after any significant change or any-significant deviation to the process or package. It should also be considered as part of the validation of any reworking, reprocessing or recovery operation.

6.31 Results of ongoing stability studies should be made available to key personnel and, in particular, to the Qualified Person(s). Where ongoing stability studies are carried out at a site other than the site of manufacture of the bulk or finished product, there should be a written agreement according to chapter 7 of the Guide. Results of ongoing stability studies should be available at the site of manufacture for review by the competent authority.

6.32 Any confirmed out of specification result, or significant negative trend, should be reported to the relevant competent authorities in accordance with chapter 8 of the Guide. The possible impact on batches on the market should be considered in accordance with chapter 8 of the Guide and in consultation with the relevant competent authorities.

6.33. A summary of all the data generated, including any interim conclusions on the programme, should be written and maintained. This summary should be subjected to self-inspection.