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On-going Stability Monitoring

The Crowne Plaza Hotel, Dublin 23rd October 2008

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Agenda

- Additions to Chapter 6 of Part 1 of EU GMP Guide
- IMB's Expectations
- Deficiencies found during inspections 2007 to 2008
- Recalls resulting from ongoing stability monitoring
- Good Practice Examples



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Additions to Chapter 6

- Came into force on 1st June 2006
- Continuous post-marketing stability programme in place capable of detecting stability issues (e.g. changes in levels of impurities or rate of dissolution)
- Monitors if product remains in specification over shelf life
- Applicable to medicinal products in commercial packs
- Bulk products if stored for long periods before packaging
- Consideration given to intermediates stored & used over long periods



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Additions to Chapter 6

- On-going Stability Programme described in Protocol following guidelines given in Chapter 6
- Protocol should extend to end of shelf life
- Results formalised in a Report
- Stability chambers qualified and maintained as per Chapter 3 & Annex 15



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Additions to Chapter 6

- Content of Stability Protocol
 - Number of batches, strength, batch size
 - Physical, chemical microbiological & biological test methods
 - Acceptance Criteria
 - Reference to test methods
 - Description of container/closure system
 - Description of storage conditions (Standardised ICH conditions)
 - Other applicable parameters specific to the product



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Additions to Chapter 6

- Protocol of on-going stability may differ from stability study submitted with MA Dossier provided justification documented in Protocol
- Number of batches and frequency of testing sufficient to allow trend analysis
- One batch per year in each strength and each primary packaging type and size (unless none produced in that year)



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Additions to Chapter 6

- For testing involving animals, the frequency of testing may take account of the risk benefit
- Bracketing & matrixing designs acceptable if scientifically justified
- Additional batches included after any significant change or deviation in the process or packaging, including any reworking, reprocessing or recovery operations



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Additions to Chapter 6

- Results of on-going stability available to QP and other key personnel
- Technical agreement in place when site of testing different from manufacturing site
- Results of on-going stability available at site of manufacture for review by the IMB
- Out of specification or atypical trends investigated



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Additions to Chapter 6

- Any confirmed OOS result or significant negative trend reported to IMB.
- Possible impact on batches on the market considered in the context of Chapter 8 and in consultation with IMB.
- A summary of all data generated, including interim conclusions on the stability programme should be written and maintained.
- This summary should be subject to periodic review.



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IMB's Expectations

- Programme being put in place if not previously established
- Protocol per product being put in place as per 6.27
- Appropriate justification if intending to do less than recommended in 6.29



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IMB's Expectations

- Effective procedures for communication and review of results, including by QP
- Effective procedures for communication of OOS results & adverse trends to Competent Authorities
- Inspection of storage and testing if at site of manufacture
- Results and trends reviewed routinely at future inspections



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IMB's Expectations

- Conduct of programme at external lab., including non-EEA based, acceptable
- Verification of GMP compliance of contract lab. rests with manufacturer. Audit report may be inspected
- IMB inspection of contract lab. Possible in certain circumstances



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Deficiencies found during Inspection

- There was no documented requirement for out of specification stability results to be notified to the IMB.
- Statements relating to stability data were not appropriately referenced or relevant trends discussed.
- Confirmed stability failures had not been communicated to the relevant Competent Authorities.
- There was no technical agreement in place with the site responsible for producing stability data.



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Deficiencies found during Inspection

- The market stability monitoring protocols reviewed during the inspection were not sufficiently detailed in regard to:
 - Rationale used to establish the number of batches to be tested per year per strength per container.
 - Justification for any changes to the testing intervals and tests to be performed compared to those described in the marketing authorisation dossier.
 - The reference to the acceptance criteria, i.e. the stability specification limits was not clearly defined.
 - The registered shelf life of the product in the various markets was not stated in all cases.



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Deficiencies found during Inspection

- The ongoing stability programme was considered to be deficient in that:
 - The stability of the bulk product was not taken into consideration as part of the assessment of the finished product shelf life after storage of maximum duration as a bulk product.
 - The process for the review of stability data from data generated by a 3rd party was not defined in a procedure.
 - In cases where a confirmed OOS was identified during ongoing stability testing, the SOP did not specify that the relevant competent authority (including the supervisory authority) be notified.
 - Responsibilities with regard to stability testing were not clearly defined in the technical agreements reviewed.

Deficiencies found during Inspection

- The evaluation of out-of-specification (OOS) results with the UV spectrometry test method for ABCD on stability studies was deficient in that:
 - The observation of OOS results was assumed to be attributed to a known potential impurity XX yet analysis of stability samples was not conducted to confirm the hypothesis.
 - Trending of analytical results were not conducted.
 - Results of the UV spectrometry test method were communicated to and approved by the QP, in the stability reports, based upon a statement of conformance/non-conformance with the test method instead of the actual analytical results obtained.



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Deficiencies found during Inspection

- The market stability-monitoring programme was deficient of the following reasons:
 - Apart from XYZ no batches of other products which had been manufactured in 2006 and 2007 had been placed on stability.
 - The market stability protocol reviewed only covered one product, ABCD and the protocol did not specify the requirement to place at least one commercial batch per year on stability.



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Deficiencies found during Inspection

- There was no technical agreement in place with the site responsible for producing stability data.
- No temperature and humidity mapping studies had been carried in the 25 degree C 60% RH stability cabinet.
- Market stability studies had not been conducted and no stability protocols were available for review during the inspection.
- The allowed testing period for the 1 year stability test point for batch ABCD had been exceeded. No deviation had been raised in relation to this.



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Deficiencies found during Inspection

- Appropriate arrangements where not in place for on-going stability monitoring of medicinal products in that the technical agreement between AA and BB identified AA as responsible for product stability testing yet there were no facilities at AA for storage or testing of stability samples.



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Deficiencies found during Inspection

- Qualification of the 25 deg C / 60% RH Stability Chamber was considered deficient in that:
 - The fan speed of the stability chamber could be varied from 0-100% in 10% increments, however, the actual setting for this variable was not recorded in the OQ documentation for the cabinet.
 - The acceptance criteria were based on average readings over a 24 hour period but did not describe acceptance criteria for the individual time point readings.



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Deficiencies found during Inspection

- On-going stability monitoring programme not in place or deficient
- No protocols or reports available
- Products not included on stability monitoring programme
- No scientific justification for reduced testing frequencies for certain products



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Deficiencies found during Inspection

- No procedures for reporting stability failures or adverse trends to QP and Regulatory Authorities
- Confirmed stability failures not reported to QP or Authorities
- Responsibilities for on-going stability programmes not covered in technical agreements



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Overview of Recalls

- 45 Quality Defect Reports in 2007 due to stability issues (human & veterinary medicinal products).
- 36 related to confirmed OOS identified during ongoing stability studies.
- 3 resulted in recalls.



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Best Practice Examples

- Timely initiation of the stability study.
- Prompt assessment of results from ongoing stability studies.
- Prompt follow up of OOS & Out of Trend (OOT) results.
- Use of Quality Risk Management when assessing results (OOS & OOT) of ongoing stability studies in line with ICH Q9.



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Best Practice Examples

- Need for the QP to be familiar with the results of ongoing stability programme.
- QP should take into account the most recent review of the ongoing stability programme for the product when performing batch certification.



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