LÆGEMIDDEL STYRELSEN

DANISH MEDICINES AGENCY

PAT EU Regulatory Update: The Inspectors View

May 20, 2008, ISPE Nordic Conference

LÆGEMIDDEL STYRELSEN

DANISH MEDICINES AGENCY

Claus Mortensen, Medicines Inspector

Member of the EMEA PAT team

Division for Inspection, Laboratories and Enforcement

Danish Medicines Agency

Issues covered

- Reviewing the status of the work of the EMEA PAT team
- Expanding on inspection issues with PAT submissions
- How to improve regulatory compliance to drive success into your PAT processes

PAT definition

A system for designing and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes for raw and in-process materials and also processes with the goal of ensuring final product quality

Reviewing the status of the work of the EMEA PAT team – who are we?

- EMEA representatives
- Regulatory people form European health authorities
- Inspectors from European health authorities

The group was established end of year 2003, and

Meetings, four times a year, take place at the EMEA, London, UK

Reviewing the status of the work of the EMEA PAT team - company specific issues

- Meetings with a number of companies at the EMEA
- Review of a number of mock and draft submissions
- Answering questions related to the above submissions and answering more general questions related to PAT
- EMEA PAT team has visited a number of companies
- EMEA PAT team participation in one PAT related inspection (pre-approval)

Reviewing the status of the work of the EMEA PAT team – other contacts

- Teleconferences with the FDA
- EFPIA (mock application, seminar including company visits)
- ASTM

Reviewing the status of the work of the EMEA PAT team – guidelines/documents

- PAT submission guide (reflection paper) on the EMEA website.
- Identification of the need for revision of regulatory and GMP related documents (guideline on parametric release and annex 17 of the EU GMP guideline; annex 15 of the EU GMP guideline and validation guidelines (continuous validation); revision of training guideline for GMP inspectors and conduct of inspections of pharmaceutical manufactures in the compilation of community procedures

Reviewing the status of the work of the EMEA PAT team – other issues

- Impact of PAT on EP and sampling and testing
- Impact of PAT on batch release
- Impact of PAT on inspection practise
- Impact of PAT on assessment practise

(all initiated in 2007)

- Training of EMEA PAT team (training courses, company visits)

Expanding on inspection issues with PAT submissions – qualifications of inspectors

- General skills:
  - GMP knowledge
  - Audit skills
  - (Review of a submission)

Expanding on inspection issues with PAT submissions – qualifications of inspectors

- More specific skills/knowledge concerning:
  - PAT instruments (NIR, Raman etc.)
  - Quality by Design
  - Design space
  - Design of experiments
  - Multivariate analysis
  - Risk assessment

Expanding on inspection issues with PAT submissions – focus points of inspections

- Prediction algorithms for parameters (e.g. dissolution of tablets):

e.g.:

- Tablet hardness
- Surface area of active substance
- Other critical factors

Expanding on inspection issues with PAT submissions – focus points of inspections

- In-depth review of equipment and other factors affecting/determining prediction algorithms:
  - Qualification and calibration of equipment
  - Maintenance of equipment
  - Is equipment mentioned in the submission the same as the equipment on site
  - Are determinations valid (e.g. surface area of raw materials as critical parameters determining dissolution)

Expanding on inspection issues with PAT submissions – focus points of inspections

- Other issues:
  - Verification on site of information in the submission (design space, specifications, data verification etc.)
  - handling of OOS results and deviations in the manufacturing process
  - computerised systems
  - suppliers of active substances and excipients
  - training of employees
  - Sampling (at-line)/cleaning of sampling devices

Expanding on inspection issues with PAT submissions – SMF

- Submission of a Site Master File with PAT related information prior to the inspection is appreciated

How to improve regulatory compliance to drive success into your PAT processes

- Planning using appropriate tools:
  - PAT instruments (NIR, Raman etc.)
  - Design of experiments
  - Multivariate analysis
  - Risk assessment, ICH Q9
  - ICH Q8 and ICH Q10

How to improve regulatory compliance to drive success into your PAT processes

- Other issues:
  - Quality and storage of development data
  - The other earlier-mentioned inspection focus points
  - Regulatory flexibility (design space, protocols)
  - Variation to approved product versus new application
  - Approach regulatory authorities in the early phases and later

PAT EU Regulatory Update: The Inspectors View

- Contact the EMEA PAT team – you are welcome!

My e-mail: cmo@dkma.dk

Useful information on EMEA website:

(**www.emea.europa.eu)**