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Regulatory milestones in EU with respect to PAT

Christina Graffner, Medical Products Agency, Uppsala, Sweden

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Process control during running manufacture instead of testing the sampled, finished product?

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European Organisation for Quality (EOQ, III/91)

Parametric release is a system of release that gives the assurance that the product is of the intended quality based on information collected during the manufacturing process and on the compliance with specific GMP requirements related to parametric release.

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European Pharmacopoeia 5th Ed.

..The manufacturer may obtain assurance that the product is of Pharmacopoeia quality from data derived, for example, from validation studies of the manufacturing process and from in-process controls. **Parametric release** in circumstances deemed appropriate by the competent authority is thus not precluded by the need to comply with the pharmacopoeia….

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Note for Guidance on Parametric Release (CPMP/QWP/3015/99)

Annex 17 to the EU Guide to GMP
(ENTR/6270/00)

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..results of in process tests and controls may constitute sufficient grounds for batch release and provide greater assurance of the finished tablet meeting certain criteria in the specification without the tests being repeated on a sample of the finished product...

Note for Guidance on Parametric Release (CPMP/QWP/3015/99)

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Guideline with focus on

- replacing sterility test on finished product
- introduction following a variation when more experience is gained

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…use of PAC, such as NIR and Raman spectroscopy, usually used in combination with multivariate analysis. Spectral data monitored on-line controlling content of active substance, polymorphism, water content, blending homogeneity, particle/powder properties or film thickness could thereby replace end-product testing like e.g. uniformity of content, tablet strength and drug dissolution...

Note for Guidance on Parametric Release (CPMP/QWP/3015/99)

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PAT is not just new technologies. The important focus is process understanding.

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Note for guidance on Development Pharmaceutics (CPMP/QWP/155/96)

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Pharmaceutical development studies to ...

...identify formulations and processing aspects crucial for quality reproducibility of batch and dosage units

Note for guidance on Development Pharmaceutics (CPMP/QWP/155/96)

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Focus on crucial properties

– constituents (API and excipients)
– stages of manufacturing process
– appropriateness of equipment and test methodology

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Statistical experimental design and multivariate analysis in dossiers

- for identifying interacting factors between active substance/s, excipients and production method that might be critical for the quality of the product
- in stability studies
- in dissolution studies

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Process development studies are the basis for process optimisation and validation requirements

Note for guidance on Development Pharmaceutics
(CPMP/QWP/155/96)

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Outcome from development

Manufacturing process in which all relevant steps *) and conditions *) are prescribed and controlled in such a way as to guarantee a finished product conforming to the specified quality.

*) with defined acceptable tolerance limits.

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Qualification and Validation: Principle

.. identify what validation work is needed to prove control of critical aspects of particular operations. Significant changes to facilities, equipment and processes, which may affect quality of product, should be validated. A risk assessment approach should be used to determine the scope and extent of validation.

Annex 14 to the EU Guide to GMP (July 2001)

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Joint QWP/Ad Hoc GMP Inspectors Team for PAT formed in November 2003

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General objective for Joint Team of QWP/Ad Hoc GMP Inspectors

Forum for dialogue and understanding between assessors and inspectors to prepare a harmonised approach within EU on assessment of applications and inspections of systems/facilities including new approaches to manufacturing and control of active substance, medicinal product, packaging material etc.

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Examples on specific objectives

- Review legal and procedural implications on EU regulatory system
- Review and comment on documents produced by other organisations
- Review and assess “mock” submissions of applications using PAT

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Examples on specific objectives
(cont.)

- Develop procedure for assessment of PAT related applications involving a co-ordinated approach by assessors and inspectors
- Avoidance of disharmony with other regional approaches
- Identify training needs

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- Draft guideline ICH Q8: Pharmaceutical Development

- Draft guideline ICH Q9: Quality Risk Management

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