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Pre-Authorisation Evaluation of Medicines for Human Use

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

CONCEPT PAPER/RECOMMENDATIONS ON THE NEED FOR A (CHMP) GUIDELINE ON THE VALIDATION OF BIOANALYTICAL METHODS

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END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 March 2009

Comments should be provided using this template template to EWPSecretariat@emea.europa.eu

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1. INTRODUCTION

Measurements of drug concentrations are an important part of the data included in medicinal products applications. This can be as part of new drug or generic applications, but also to support variations. Moreover, critical decisions are made based upon drug concentrations, like in bioequivalence studies and interaction studies. Therefore the applied bioanalytical methods used must be well characterised, fully validated and documented to yield reliable results that can be satisfactorily interpreted. However, no CHMP guidance is available on this topic.

2. PROBLEM STATEMENT

The CHMP does not have a Note for Guidance on validation of bio-analytical methods, although analytical methods and validations are included in most application dossiers. The new guideline will provide recommendations for the validation of a bioanalytical method. Next to that, specific topics should be addressed with regard to the bioanalytical method, i.e. the actual analysis of study samples.

Furthermore it is not the purpose of the new guideline to introduce fully new criteria, but it should be in line with current scientific knowledge on this topic.

3. DISCUSSION

The Note for Guidance on the validation of bioanalytical methods will apply to Marketing Authorisation Applications for human medicinal products submitted in accordance with the Directive 2001/83/EC as amended, in which the analysis of drug concentrations is part of the application.

The topics to be included in this guidance are:

Good Laboratory Practice (GLP).

Which conditions should be applied and can be requested. Attention will be paid to quality control and quality assurance system.

Complete validation of an analytical method

The main objective of method validation is to demonstrate the reliability of a particular method for the quantitative determination of an analyte concentration in a specific biological matrix, like blood, plasma or urine. The main characteristics of a bioanalytical method essential to ensure the acceptability of the performance and the reliability of analytical results are:

- specificity; sensitivity, the response function (calibration curve performance), accuracy, precision, recovery, dilution integrity, stability of the analyte(s) in the biological matrix and the stock solutions under processing conditions and during the entire period of storage, and robustness.

- **Reference standards**

Criteria to ensure the quality and/or purity of the reference standards and possible internal standards will be provided in .the guideline

Regarding **validation of the analytical method** the following issue will be included:

- **Specificity**

How to evaluate specificity, not only with regard to the matrix, but also with regard to interference by metabolites of the drug(s) applied, or interference of degradation products formed during sample preparation, and interference of possible co-medications.

- **Sensitivity**

How to determine and which criteria should be applied to:

- Limit of detection

- Lower limit of quantitation

- **Calibration curve**

Evaluation of the response of the instrument with regard to the analyte will be included. Furthermore attention will be paid what criteria should be applied with regard to accuracy and precision of the standards (back calculated concentrations).

- **Accuracy**

How many quality control samples (QC samples) should be used to evaluated accuracy. Which criteria should be applied: the following will be included:

- Intra- or within-run accuracy

- Inter- or between –run or –day accuracy

- **Precision**

In addition to accuracy, criteria on precision will be included, taking into account:

- Intra-or within-run precision

- Inter- or between –run or –day precision

Furthermore attention will be paid to dilution integrity.

- **Recovery**

Evaluation of the recovery will be included.

- **Stability**

How to evaluate the stability of the analyte(s) to ensure that every step taken in sample preparation and during sample analysis does not affect the concentration of the analyte significantly.

Which criteria should be applied.

Attention will be paid to:

- freeze and thaw stability of the analyte in the matrix from freezer storage conditions to room temperature

- stability of the analyte in matrix stored in the refrigerator

- bench top stability of the analyte in matrix at room temperature

- long term stability of the analyte in matrix stored in the freezer

- bench top stability of the processed sample at room temperature (dry extract or in the injection phase)

- in-injector stability of the processed sample at injector temperature

Furthermore, evaluation of the stock solutions will be taken into account.

- **Robustness**

How to consider robustness during the development and application phases of an analytical method with regard to e.g. instrument, operator or site changes.

- **Matrix effects**

Evaluation of matrix effects in LC/MS/MS methods will be included.

Next to the complete validation, attention will be paid to:

- cross validation;
- partial validation.

Bioanalytical method: analysis of (study) samples

How to set up an analytical run.

What acceptance criteria for an analytical run should be applied (accuracy and precision).

Reanalysis of subject samples

When may subject samples be reanalysed.

What should be reported.

Reintegration of chromatograms

How to deal with reintegration.

Study report

Which reports should be provided.

What should be included in the validation report.

What should be included in the analytical report.

4. RECOMMENDATION

The Efficacy Working Party (EWP) recommends preparing a Guideline on the validation of bioanalytical methods as no European guidance exists in this area.

5. PROPOSED TIMETABLE

It is anticipated that a draft CHMP document may be released 8 months after adoption of the Concept Paper. The draft document will then be released for 6 months of external consultation and following the receipt of comments it will be finalised within approximately 6 months.

6. RESOURCE REQUIREMENTS FOR PREPARATION

The preparation will involve the EWP Therapeutic subgroup on Pharmacokinetics (PK-EWP), with the contribution of the GCP and GLP Inspectors Working Groups.

7. IMPACT ASSESSMENT (ANTICIPATED)

Introducing a new guideline will be of benefit for industry, as no such guideline exists in EU. Moreover, it may lead to a consistent assessment between different Member States.

8. INTERESTED PARTIES

Industry and bioanalytical laboratories.