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Short communication

Re-validation during method transfer examples in Official medicines control laboratories

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Introduction

Method transfer represents a completely documented process which covers transferring of analytical methods from the originating laboratory which developed and validated the method, to the receiving laboratory for quality control of medicines. The method transfer, is an experimental demonstration that the receiving laboratory, can perform the method accordingly to its use. Successful transfer of a method should prevent the placing on the market of a medicine which does not conform to the quality specification, as well as to avoid the rejection of a medicine whose quality conforms to its specification.

The common practice of method transfer, requires verification of the method established by the manufacturer, from the competent authority/official medicines control laboratory, or in case of change of the method outside the acceptable limits, it is necessary to carry out re-validation. Depending on the scope of the changes, re-validation can be complete or partial, using appropriate validation parameters.

In this paper, two examples of method transfer including partial re-validation are presented for: dissolution using a spectrophotometric method for quantification and determination of related substances using HPLC method with gradient elution.

Examples of partial re-validation during method transfer

Example 1: Method transfer with partial re-validation for dissolution of valsartan/hydrochlorothiazide film-coated tablets (80 mg/12.5 mg and 160 mg/12.5 mg) using UV-spectrophotometric method

The method from the originating laboratory defines an on-line dissolution test using a UV-spectrophotometer with a 1 mm cell. Many of the Official medicines control laboratories are equipped with off-line disolution testing unit, and in case of spectrophotometric determination, a standard cuvette of 1 cm. With the proposed concentration of the standard and sample solutions, the obtained absorbances with the 1 cm cuvette, exceed the linearity range of the used equipment (Agilent 8453 UV-Vis spectrophotometer). In order to acquire adequate values for the measured absorbance, the concentration of the soluitions was adjusted.

According to the ICH Q2(R1) quideline for validation of analytical procedures, the nature of the change demands partial re-validation on the parameter linearity. The linearity was evaluated for both active substances in the range of 30 - 120% of the working concentration (0.053 mg/mL for valsartan and 0.0083 mg/mL for hydrochlorothiazide), on both wavelenghts, as required in the proposed method (250 nm and 272 nm).

The results from the re-validation confirm the linearity of the method in the chosen concentration range, according to the requirements of the ICH Q2(R1) quideline (for valsartan, correlation coefficents (R^2) of the regression lines were 1.0000 and 1.0000, respectively for wavelength 250 nm and 272 nm; for hydrochlorothiazide, R^2 of the

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regression lines were 0.9994 and 0.9996, respectively for wavelength 250 nm and 272 nm).

The results from the dissolution test of both dosage forms were within the specification limit.

Example 2: Method transfer with partial re-validation for determination of related substances of fingolimod in hard capsules using HPLC method with gradient elution

The method from the originating laboratory, for related substances of fingolimod, proposes usage of the chromatographic column XTerra MS C8 50 x 4.6 mm, 2.5 µm. The OMCL, Center for Drug Quality Control_MK, used an available column with similar properties of the stationary phase and similar dimensions, Poroshell 120 EC-C8 50 x 4.6 mm 2.7 µm, taking into account that due to the vast offer of chromatographic columns on the market, very often the OMCLs do not have the columns proposed in manufacturer methods at their disposal.

In order to achieve the system suitability requirements, an adjustment of the flow rate was required. The final chromatographic conditions under which system suitability was obtained, included flow rate of 1.9 mL/min instead of 1.5 mL/min, under gradient elution. According to the permited adjustments of the chromatographic conditions for gradient elution (Ph.Eur. 2.2.46), the change of the flow rate, the change from Totally Porous Particle (TPP) column to Superficially Porous Particle (SPP) column and the change of the particle size of the column, and are outside of the specified limits.

Partial re-validation due to the nature of the change was performed on the parameters: specificity, limit of quantification, system precision and accuracy on the concentration level equal to the specification limit of unknown impurity (1.0%). Specificity in regard to placebo solution was confirmed, as well as the proposed limit of quantification of 0.1%. Results for system precision were RSD = 0.5%, and for accuracy on the concentration level equal to the specification limit of unknown impurity (1.0%), recovery was 100.38% ± 1.6 % (95% level of confidence). The results from the re-validation are in line with the requirements of the ICH Q2(R1) quideline.

The results from the testing of the related substances of fingolimod in the dosage form were within the specification limits.

Conclusion

The examples for partial re-validation of the methods during method transfer are a common practice for the receiving laboratory. The laboratory work regarding re-validation is a demanding and time-consuming process. With the current practice for pharmacopoeial harmonization, regarding the analytical techniques, and the announced harmonized text for chromatographic techniques, Ph.Eur. 2.2.46, which will be officially published on January 1st of 2023, in the 11th edition of the European Pharmacopoeia, re-validation waiver of the methods is proposed, which will greatly facilitate the laboratory work.

For some analytical techniques, the need for re-validation remains necessary, as is the example with the partial re-validation of the spectrophotometric method, using a different length of the used cuvette.

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