RE-VALIDATION DURING METHOD TRANSFER EXAMPLES IN OFFICIAL MEDICINES CONTROL LABORATORIES

Marija Zafirova Gjorgievska, Gabriela Petrovska-Dimitrievska, Vasil Karchev, Hrisanta Godzo, Olga Gigopulu, Liljana Ugrinova

Ss. Cyril and Methodius University - Faculty of Pharmacy, Skopje

INTRODUCTION

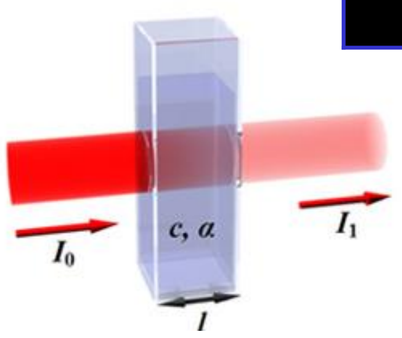
Method transfer represents a completely documented process which covers transferring of analytical methods from the originating laboratory which developed and validated the method, to the receiving laboratory for quality control of medicines. The method transfer, is an experimental demonstration that 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.

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

Method from originating laboratory	• On-line dissolution test using a UV-spectrophotometer with a 1 mm cell	**Reason for change during method transfer in receiving laboratory**	• OMCL, CDQC_MK* is equipped for off-line disolution testing, using a UV-spectrophotometer, with a standard cuvette of 1 cm; • With proposed concentration of standard and sample solutions, obtained absorbances with 1 cm cuvette, exceed the linearity range of used equipment (Agilent 8453 UV-Vis spectrophotometer)	**Change made in final method in receiving laboratory**	• Concentration of the solutions was adjusted in order to acquire adequate values for the measured absorbance



Partial re-validation required according to the ICH Q2(R1)**

Partial re-validation parameters				
LINEARITY (linearity range: 30 - 120% of the working concentration)	**Valsartan** (working concentration = 0.053 mg/mL)		**Hydrochlorothiazide** (working concentration = 0.0083 mg/mL)	
Measuring Wavelength	**250 nm**	**272 nm**	**250 nm**	**272 nm**
Correlation coefficent (R2)	1.0000	1.0000	0.9994	0.9996

The results from the re-validation confirm the linearity of the method in the chosen concentration range. 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

Method from originating laboratory	• Uses chromatographic column, XTerra MS C8 50 x 4.6 mm 2.5 µm	**Reason for change during method transfer in receiving laboratory**	• Due to vast offer of chromatographic columns on the market, OMCL, CDQC_MK does not have the exact same column at its disposal; uses 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; • Due to column change, in order to achieve system suitability requirements, an adjustment of the flow rate is required.	**Change made in final method in receiving laboratory**	• OMCL, CDQC_MK uses chromatographic column, Poroshell 120 EC-C8 50 x 4.6 mm 2.7 µm (change from Totally Porous Particle (TPP) column to Superficially Porous Particle (SPP) column and change of the particle size of the column) • Due to column change, in order to achieve system suitability requirements, flow rate of 1.9 mL/min instead of 1.5 mL/min, under gradient elution, was used.

Partial re-validation required according to the permited adjustments of the chromatographic conditions for gradient elution (Ph.Eur. 2.2.46)

Partial re-validation parameters (according to the ICH Q2(R1))	Results
Specificity	specificity in regard to placebo solution was confirmed
Limit of quantification (LOQ)	proposed limit of quantification of 0.1% was confirmed
System precision	RSD = 0.5%
Accuracy (on the concentration level equal to the specification limit of unknown impurity (1.0%))	Recovery = 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 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.

*Official medicines control laboratories, Center for Drug Quality Control_MK
**ICH Q2(R1), quideline for validation of analytical procedures

References

1.European Pharmacopoeia (Ph. Eur.) 10th Edition, Council of Europe, Strasbourg, France, 2019.
2.International Conference on Harmonization Technical Requirements for Registration of Pharmaceuticals for Human Use. Guideline on Validation of
3.Analytical Procedures: Text and Methodology Q2(R1). Geneva, Switzerland, 2005.
United States Pharmacopoeia-National Formulary (USP–NF) 2022 Issue 1, United States Pharmacopeial Convention, Rockville, USA, 2021.