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Review

The transfer of analytical procedures

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ABSTRACT

Analytical method transfers are certainly among the most discussed topics in the GMP regulated sector. However, they are surprisingly little regulated in detail. General information is provided by USP, WHO, and ISPE in particular. Most recently, the EU emphasized the importance of analytical transfer by including it in their draft of the revised GMP Guideline. In this article, an overview and comparison of these guidelines is provided.

The key to success for method transfers is the excellent communication between sending and receiving unit. In order to facilitate this communication, procedures, flow charts and checklists for responsibilities, success factors, transfer categories, the transfer plan and report, strategies in case of failed transfers, tables with acceptance limits are provided here, together with a comprehensive glossary. Potential pitfalls are described such that they can be avoided.

In order to assure an efficient and sustainable transfer of analytical procedures, a practically relevant and scientifically sound evaluation with corresponding acceptance criteria is crucial. Various strategies and statistical tools such as significance tests, absolute acceptance criteria, and equivalence tests are thoroughly descibed and compared in detail giving examples. Significance tests should be avoided. The success criterion is not statistical significance, but rather analytical relevance. Depending on a risk assessment of the analytical procedure in question, statistical equivalence tests are recommended, because they include both, a practically relevant acceptance limit and a direct control of the statistical risks. However, for lower risk procedures, a simple comparison of the transfer performance parameters to absolute limits is also regarded as sufficient.

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Glossary

α	error probability
AI	acceptance interval, see relevance interval
AL	acceptance limit
%AL	scaled standard error of the mean between laboratories (Section 4.4.3, Eq. (10))
API	active pharmaceutical ingredient
ATT	analytical transfer team
CI	confidence interval
C_L	lower confidence limit
C_U	upper confidence limit
df, ϑ	degrees of freedom
DP	drug product
ε	acceptable deviation
EMA	European Agency for Evaluation of Medicinal Products
H_0	null hypothesis
H_1	alternative hypothesis
ISPE	International Society of Pharmaceutical Engineering
μ	true mean value
n_i	number of data of the ith data set
RI	relevance interval
RSD%	percent relative standard deviation
RU	receiving unit, also called routine unit (site/laboratory))
SD, $\hat{\sigma}$	standard deviation
$\hat{\sigma}_i$	SD of the ith data set
$\hat{\sigma}_p$	pooled SD
$\hat{\sigma}_{\bar{x}}$	standard error of the mean between laboratories
SOP	standard operating procedure
SU	sending unit, also called developing/reference/originating unit/lab/site
TSD	target standard deviation
T_t	statistic of a *t*-test (Eq. (1))
t	tabled values of *t*-distribution
θ	measured parameter (equivalence test)
θ_0	reference value (equivalence test)
USP	United States Pharmacopeia
WHO	World Health Organization
$\bar{x}_i$	mean value of the ith data set

1. Introduction

The subject of method transfer certainly belongs to the most discussed and complex issues in the GMP regulated sector. It is regularly examined in audits and inspections which underlines its relevance and importance. An analytical method is transferred from a sending unit (SU) to the receiving unit (RU). The sending unit is the laboratory, where the method was originally developed and validated and/or routinely applied. The receiving unit is another laboratory, which is close to an additional production site or a contract laboratory. Obviously transfers of analytical methods are important issues during the life cycle of a product [1].

Nevertheless, the implementation of correct and efficient transfer processes is still far from being part of daily laboratory routine. This is also the reason for the European Agency for Evaluation of Medicinal Products (EMA) to include this topic in the draft of revision of Chapter 6 of the EU GMP Guideline [2].

The appropriate organization of analytical method transfer is an essential part of the quality assurance system, when pharmaceuticals are produced and analyzed at different sites.

As the cGMP requirement 21CFR §211.165 states: "The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the company shall be established and documented" [3]. 21CFR §211.194 requires, that "The suitability of all testing methods shall be verified under actual conditions of use" [4]. This can only be ensured by on-site validated procedures or verified compendial methods or by successful method transfers.[2]

The goal of the transfer activities is to demonstrate the ability of the RU to perform the relevant analytical procedures successfully. It has to be pointed out that the performance and ability of the sites is always the sum of the ability of the staff and the performance characteristics of their equipment and should not depend on the properties or quality of the samples.

However the lack of explicit regulatory guidance in the past (with the exception of the recommendations of the ISPE Guideline [5] and has led to a multitude of empirical procedures that differ very much in the validity of their results. An improved general concept for the implementation in daily laboratory practice is therefore urgently needed.

[2] In order to facilitate the readability, the terms "method" and "analytical procedure" are used synonymously. All analytical steps are included, such as sample preparation, analytical methodology, calibration, reportable result, etc.

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