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Review article / Обзорная статья

Transfer of Impurities Determination Methods: Comparative Testing, Validation, Acceptance Criteria (Review)

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Abstract

Introduction. Different approaches are used for transfer of impurities determination methods. In most cases, comparative testing of samples or partial validation of methods is performed. At the same time, a number of issues important for practice are still relevant.

Text. The features of methods validation and comparative testing of samples during the transfer of impurities determination methods are considered. Potential acceptance criteria – requirements to the permissible difference between results of transmitting and receiving laboratories – are given. The calculation formulas of the TOST test are considered, and the critical condition for the comparative testing of samples is given. The key points that should be taken into account when transferring the methods are discussed.

Conclusion. The data and recommendations are presented, which are important for increasing the reliability of the transfer of the impurities determination methods.

Keywords: methods transfer, impurities, acceptance criteria, comparative testing of samples, validation

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Трансфер методик определения примесей: сравнительное испытание, валидация, критерии приемлемости (обзор)

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Резюме

Введение. При трансфере методик определения примесей используют различные подходы. В большинстве случаев проводят сравнительное испытание образцов или частичную валидацию методик. При этом до сих пор остается актуальным ряд важных для практики вопросов.

Текст. Рассмотрены особенности валидации методик и сравнительного испытания образцов при трансфере методик определения примесей. Приведены потенциальные критерии приемлемости – требования к допустимому различию результатов передающей и принимающей лабораторий. Рассмотрены расчетные формулы теста TOST и приведено критическое условие для сравнительного испытания образцов. Обсуждены ключевые моменты, которые следует учитывать при трансфере методик.

Заключение. Представлены данные и рекомендации, которые важны для повышения надежности трансфера методик определения примесей.

Ключевые слова: трансфер методик, примеси, критерии приемлемости, сравнительное испытание образцов, валидация

Конфликт интересов. Автор декларирует отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Вклад авторов. Автор участвовал в сборе информации, ее анализе и в написании текста статьи.

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INTRODUCTION

Transfer of analytical methods – a documented procedure that provides powers to the laboratory of accepting party to use analytical methods developed in the laboratory of the transferring party [1]. Nowadays, dozens of guidances and reviews of transfer of analytical methods have been published. As a rule, they review regulatory and organizational aspects of transfer of analytical procedures, for example [1, 2][1]. Meanwhile problems related to the selection of the method for the transfer of procedures and acceptability criteria for the method of impurity quantification still remain challenging – requirements to the acceptable difference between the results of transferring and accepting parties.

Aim of the article is to review particularities of validation of procedures and comparative test of samples in transfer of methods for determination of impurities; discussion of acceptability criteria and key aspects which may influence transfer results.

The US Pharmacopeia, section <1224> Transfer of analytical procedures provides the following methods for transfer of analytical procedures [4].

1. *Comparative Testing* – comparative test of samples of the same batches of a drug product (a drug, pharmaceutical substance) or simulated samples (for guaranteed homogeneity of analyzed objects) in the transferring and accepting laboratories.
2. *Covalidation* – covalidation of procedures by transferring and accepting laboratories. In covalidation, a transferring party engages employees of the accepting party for validation on its territory [1].
3. *Partial revalidation* – partial validation of a procedure (verification of validation characteristics) in the accepting laboratory.
4. *Revalidation* – a full validation (revalidation) of a procedure in the accepting laboratory.

Transfer Waiver is the alternative to methods 1–4 – a decision not to transfer an analytical method just only to verify the procedure [4]. Corresponding conditions and possible actions are given in the special section of the US Pharmacopeia <1226> Verification of compendial procedures [4]. Several important moments should be stated. Verification without any partial procedure validation is applicable only for compendial methods for quality control of pharmaceutical substances. The cause is a possible influence of a difference between excipients in case of drug products. As for methods for determination of impurities, the method should meet the compendial procedure not only for sample preparation and chromatographic conditions but also for a certain chromatographic column which is given in the transferred procedure[2]. Allowable adjustments of chromatographic conditions given in the US Pharmacopeia (USP), European Pharmacopeia (EP) and State Pharmacopeia XIV [4–6] should be treated with caution. It has appeared that some of the corrections are not applicable for methods for determination of impurities. The problem and methods for its solution are detailed in [7].

Method 1 is used is most cases for transfer of methods for impurity quantification (hereinafter – the method for determination of impurities) as it is the simplest and intuitively clear. Method 3 is less used. Methods 2 and 4 are used rarely as they are time and resource consuming. When any method is used for transfer of procedures, the compliance of the chromatographic system requirements is first checked. Only then if a positive result is obtained, works are performed on comparative testing of samples or partial, or full method validation.

Partial validation (verification of validation characteristics) in transfer of methods

Full validation of a method in the accepting laboratory may be required only in the extreme case. As a rule, partial method validation is sufficient, i.e. verification of certain validation characteristics. We recommend to verify specificity, precision, limit of quantification LOQ.

- ***Verification of method specificity.*** Verifying method specificity, the accepting laboratory only checks if the requirements of chromatographic suitability are met, and tests separation of identified impurities. However, it is not always enough

[1] Aspects of transfer of bioanalytical procedures are detailed in the review [3].

[2] Columns for compendial monographs of the European Pharmacopeia can be found in Knowledge Database: https://extranet. edqm.eu/publications/recherches_sw.shtml, and for US Pharmacopeia in the database: http://www.usp.org/resources/ chromatographic-columns.

for identification of risks related to insufficient separation ability of the transferred method. We recommend that results of stress tests in validation documents of transferring laboratory should be carefully reviewed, First of all, stress degradation of a drug substance should not be too low – not less than the standardized sum of impurities and not too large (due to ongoing secondary processes not typical for storage conditions of a drug; the recommendations on the upper limit of degradation are given in [8, 9]. The presented chromatograms and tables of peak calculation should explicitly confirm a sufficient (acceptable) separation of impurity peaks between each other and other peaks. *To confirm acceptability of separation of a partially overlapping impurity peak, the peak-to-valley requirement can be used* $p/v \geq 1.5$ [10] or condition: or condition: a relative standard deviation of RSD of the area of a partially overlapping impurity peak should not exceed 20 % (the greatest acceptable RSD value in LOQ calculation [11, p. 24]). If results of stress tests are absent or doubtful, then it may be necessary to perform stress tests in verification of method specificity [8, 12]. However, it is the last variant. As an alternative, the analysis of samples of several batches of a drug product at the end of shelf life can be used. On chromatograms of test solutions of samples, impurity peaks should be rather well-separated between each other and peaks of a drug substance, system peaks and placebo peaks; the results of impurity determination should correspond to the standardized limits in the specification. To increase reliability of conclusions in specification of method specificity, spectral purity of a drug substance peak can be controlled on chromatograms of test solutions.

- ***Verification of method precision.*** When precision of methods for impurity determination is verified, repeatability (similarity) are usually reviewed. The typical acceptability criterion for repeatability is the requirement: a relative standard deviation of results of impurity determination RSD ≤ 5.0 %. Intermediate (intralaboratory) precision is sometimes verified. The requirements to intralaboratory precision of methods are reviewed in [13, 14].
- ***Verification of LOQ value*** is performed to check necessary sensitivity of impurity determination. LOQ value for identified impurities which contents is determined with impurity standard is usually verified. The necessary sensitivity of the method for unidentified and identified impurities determined in relation to standard of the main substance is controlled on the first stage of the method transfer – when checking the system suitability. The requirement performance is checked: signal/noise ration for baseline for the peak of the main (drug) substance S/N ≥ 10 when a solution is chromatographed to check the system suitability. It is usually sufficient. Meanwhile, it is preferable to verify correction coefficient F for identified impurities which are determined in relation to main substance standard. The methods for a correct determination of correction coefficient are detailed in [15].

The same acceptability criteria are usually used in partial method validation as in validation documentation of the transferring party. Sometimes, the accepting party may insist on other acceptability criteria. For example, on more reliable determination of LOQ of signal/noise ratio of the baseline S/N = 10 rather than on calibration plot. It is justified that it is the accepting party that will be responsible for product analysis results. Typical acceptability criteria for validation of analytical procedures are given in some reviews and books; the following are recommended [14, 16, 17].

Remark. Transfer of methods in RF and abroad differs in practice. In RF, most often, the accepting party is a mediator in transfer of methods when suitability of the method to be transferred is evaluated for product quality control. Abroad, vice versa, a transferring laboratory is usually a mediator. It checks the readiness of the accepting laboratory to reproduce the method correctly and get results within the acceptability criteria developed by the transferring laboratory. Each of the approaches has its own advantages and disadvantages.

Comparative testing of samples in method transfer

As mentioned above, the method for method transfer of is most widely used. Nevertheless, the literature analysis of transfer of analytical methods has shown that there are

only few publications which provide the requirements to the acceptable difference between the analysis results on the method for impurity determination [14, 18–22]. They are systemized in the table. It shown that uniform requirements to acceptable difference between results of the transferring and accepting laboratories are not still legalized. Due to that, the acceptability criteria given in table 1 should be reviewed as guides in transfer of methods for determination of impurities. Two types of acceptance criteria are used in transfer of methods. The first – empirical acceptance criteria, the second – statistical acceptance criteria. It is typical for methods for determination of impurities that statistical acceptance criteria are used not alone but in combination with empirical acceptance criteria; the reason will be reviewed below.

In comparative testing of samples, the results of determination of all standardized values for impurities in the specification are compared. Usually, the contents of the largest unidentified impurity, the contents of separately standardized (identified) impurities and sum of impurities are compared.

Table 1. Acceptance criteria for comparative testing of samples for transfer methods for determination of impurities

№	Empirical acceptance criteria
1	The difference between the average results of determining the content of impurities (above LOQ) between the receiving and transmitting laboratories for each sample should not exceed: **±50 %** (relative) for impurities <0.1 %; **±40 %** (relative) for impurities ≥0.1 % and <0.5 %; **±20 %** (relative) for impurities ≥0.5 % [18, p. 301]
2	For impurities <0.15 %, the deviation from the data of the transmitting unit (TU) should be within **0.04 %** (absolute value). For impurities ≥0.15 %, the deviation from the TU data should be within **30 %** (relative value). For the sum of impurities <2.0 %, the deviations from the TU data should be within **0.3 %** (absolute value). For the sum of impurities ≥2.0 %, the deviations from the TU data should be within **0.5 %** (absolute value). An example from [19, Appendix 6]
Statistical + empirical acceptance criteria *	
3	*International Society for Pharmaceutical Engineering (ISPE) recommendations* *For moderately high levels* of impurities, <use> two one-sided *t*-tests; the difference between sites <should be> **≤10 %** at a 95 % confidence level. *For low levels* of impurities, but above the desregard limit, the difference between the average values of the transmitting and receiving unuts should be within ±25 % relative or **±0.05 %** absolute [20]
4	For high levels of impurities: two one-sided *t*-tests; difference between unites **≤10 %** at 95 % confidence level. For low levels of impurities, the difference between the average values of the transmitting and receiving units should be within **±25 %** (relative) [18, p. 300]
5	*World Health Organization (WHO)* *For moderately high levels* of impurities, <use> two one-sided *t*-tests; the difference <should be> **≤10 %** for a 95 % confidence level. *For low levels* of impurities, the values of the receiving unit should be within ±25 % of the values of the transmitting unit, or the average value of the receiving unit should be within **±0.05 %** of the average value of the transmitting unit [14, 21, 22]

Note. * The relative difference between the transmitting and receiving laboratories is usually calculated relative to the transmitting laboratory.

- ***Empirical acceptance criteria are*** based on practical knowledge obtained in transfer of methods for determination of impurities. They are given as an acceptable difference between analysis results of the transferring and transferring parties in relative and/or absolute %. The advantage of empirical acceptance criteria is their suitability in low impurity levels. Meanwhile, a great subjectivity is a significant drawback of empirical acceptance criteria. It is confirmed with a greater difference of the criteria in the table.

The question *whether impurities below disregard limit should be considered in method transfer* is challenging for comparative testing of samples in method transfer. The question hereto is obtained in practice. The author is aware of the case when a mean result of determination of the unidentified impurity in the transferring party was 0.05 %, and the one of the accepting party was 0.03 %. From the practical point of view, such difference of results is negligible, acceptable. However, it was ≈40 % in relation to the transferring party. Based on the case, the corrected acceptability criterion was agreed when impurity levels are less than 0.1 %: 50 % instead of relative 25 %. It should be noted that when impurities less than 0.05 % are disregarded, the difference would be relative 100 %. Therefore, all impurities should be considered when *methods for determination of impurities are transferred* (usually, these are impurities ≥0.01 %)

regardless of the presence of disregard threshold in the method. It decreases the risk of negative transfer result in the event of nearly negligible difference in results of impurity determination.

- ***Statistical acceptance criteria*** are based on the evaluation of statistical equivalence of results obtained in various laboratories. Various approaches can be used for that. However, TOST (Two One-Sided Test) with two one-sided t-tests is most applicable for transfer of methods [14, 22–28].

TOST differs significantly from conventional Student's *t*-test (Two-sample t-test). As it appears, why not using the latter as it is intended for evaluation of statistical insignificance of differences between mean values at assigned probability. However, it has appeared in practice that classical Student's *t*-test is not applicable for transfer of methods. It may often lead to a false negative conclusion on non-equivalence of analysis results in transfer of methods [23, 27, 28]. Generally, test TOST evaluates not a statistical significance of difference between mean values at assigned probability, but difference or relative difference of mean values with a confidence interval fallen to acceptable range [14, 24, 28]. I.e. a certain practical insignificance of difference between mean values (equivalence) may occur despite statistical significance of the difference.

Table 1 provides the acceptance criterion when TOST is used for methods for determination of impurities from the guidances of the World non-commercial voluntary organization of technical specialists (ISPE) and World Health Organization (WHO):

- *For moderately high levels* of impurities, two one-sided *t*-tests are <used>; the difference between areas should be ≤ 10 % at 95% confidence probability [20, 21].

To understand the nature of the criterion and necessary calculation, we provide typical equations which are used for equivalence test TOST in transfer of methods [24]:

$$C_L = 100\left[\left(\frac{\bar{x}_1}{\bar{x}_2}\right)\cdot e^{-(t_{\alpha,(2n-2)}\cdot\hat{\sigma})} - 1\right], \quad (1)$$

$$C_U = 100\left[\left(\frac{\bar{x}_1}{\bar{x}_2}\right)\cdot e^{(t_{\alpha,(2n-2)}\cdot\hat{\sigma})} - 1\right], \quad (2)$$

$$\hat{\sigma} = \sqrt{\frac{1}{2n}(\hat{\sigma}_1^2 + \hat{\sigma}_2^2)\cdot\left(\frac{1}{\bar{x}_1^2} + \frac{1}{\bar{x}_2^2}\right)}, \quad (3)$$

where C_L and C_U – lower and upper limits (in %) of confidence interval of test TOST; $\bar{x}_1$ and $\bar{x}_2$ – mean values of analysis results; $t_{\alpha,(2n-2)}$ – a value of one-sided Student's *t*-test for error probability $\alpha = 0{,}05$ (confidence probability $P = 1 - \alpha = 0{,}95$, i. e. 95 %); n – number of analysis results in each of the laboratories in method transfer; $\hat{\sigma}_1$ and $\hat{\sigma}_2$ – standard deviations of mean values of analysis results, indexes 1 and 2 refer to laboratories 1 and 2, respectively. A threshold value of acceptable difference between areas (in this case, 10 %) is specified as $\boldsymbol{L_{\%}}$. While ***transfer of methods is considered acceptable (results of analyses are equivalent), if values C_L and C_U are in the range $-L_{\%}$ to $+L_{\%}$*** (–10 % to +10 % for the abovementioned acceptance criterion):

$$-L_{\%} \le C_L \text{ and } C_U \le +L_{\%}. \quad (4)$$

$$-10 \le C_L \text{ and } C_U \le +10. \quad (5)$$

Equations (1)–(3) show that the lower and upper limits of confidence interval of test TOST – C_L and C_U depend of the number of analyses n, mean analysis results $\bar{x}_1$ and $\bar{x}_2$ and standard deviations of mean values of analysis results $\hat{\sigma}_1$ and $\hat{\sigma}_2$. Let's review influence of the factors. First of all, it should be noted that typical (minimal) number of analyses performed by each chemist in test TOST is $n = 6$ [27, 28]. Meanwhile, more analyses may be required for more reliable conclusions [24, 27]. Our model calculations have shown that while $\hat{\sigma}$ and constant values n, $\bar{x}_1$, $\bar{x}_2$ are decreased, the difference between C_L and C_U is decreased. In a threshold case at $\hat{\sigma} \to 0$ (i. e. insignificance of random error), an exponential multiplier in equations (1) and (2) becomes equal 1. It leads to simplification of condition (4) for a positive result of the method transfer:

$$-L_{\%} \le C_L = C_U = 100\left[\left(\frac{\bar{x}_1}{\bar{x}_2}\right) - 1\right] \le +L_{\%}. \quad (6)$$

Let's deduct C_L and C_U from (6), then divide all parts of the inequality to 100 and transfer 1 to the left and right parts of the inequality; as a result, we will get *critical ratio*

of mean values of analysis results $\bar{x}_1/\bar{x}_2$ in the accepting and transferring laboratories:

$$-L+1 \le \frac{\bar{x}_1}{\bar{x}_2} \le L+1, \quad (7)$$

where L – a threshold value "of allowable difference between areas" (laboratories) expressed in unit shares (in our case $L = 10(\%)/100 = 0{,}1$).

In transfer of methods, the contribution of random errors to results of analyses is always significant. Therefore, it is necessary *for a positive result of method transfer with TOST that the ratio of mean analysis results* $\bar{x}_1/\bar{x}_2$ was not only within interval $L \pm 1$ in accordance with (7) – in our case, from 0.9 to 1.1 but was rather far from the margins of the interval. For example, $0{,}95 \le \bar{x}_1/\bar{x}_2 \le 1{,}05$.

Important particularities of test TOST for method transfer are reviewed in [27, 28]. In particular, it is recommended to evaluate preliminarily expected TOST results based on data obtained by (two chemists) while testing intralaboratory precision in the transferring laboratory in method validation [28]. When TOST is used for evaluation of result equivalence in laboratories, a justified value of maximum acceptable difference between mean (accur $\Delta_{\bar{x}_{\max,\,95\%}}$ eptance limit) [28] may be used instead of a priori acceptable difference in 10 %. For the purpose, special equations were offered. Other statistical approaches for evaluation of equivalence of analysis results as well as for methods for impurity determination were reviewed [14]. However, they all, except for TOST, were not widely used in transfer of analytical procedures.

Key aspects to be considered in transfer of methods for impurity determination

- *Chromatographic column*. In practice, the transferring party usually provides a chromatographic column to the accepting party. However, when a method is developed, a chromatographic column can be modified, and its selectivity can be changed. Therefore it is better for the accepting party to perform analyses on a new (previously not used) chromatographic column stated in the method to be transferred.
- *Contents of impurities in samples to be transferred.* The experience of method transfer has shown that the risk of a negative result can be significantly reduced with the increase of contents of the largest unidentified impurity up to the value which significantly exceeds the impurity disregard limit but is not more than its standardized limit. For that, drug samples can be artificially aged. For example, heating them in a thermostat or climatic chamber (suppositories and soft dosage forms are the exception). If necessary, identified impurities can be added; if sample homogeneity by impurity contents was preserved. It can be easily done in the event of liquid dosage forms. It should be also stated that some companies may use OOS samples (Out-of-specification) in method transfer, i. e. those in which impurity contents exceeds limits stated in the specification.

We emphasize that the situation is incorrect when the contents of standardized impurities in samples provided for method transfer is less that the disregard limit of impurities, and such impurities are neglected. It also refers to drug samples analyzed in the test of method precision being part of its validation. The article author has found such situations for several times in expertise of validation documentation and method transfer protocols. It is an important moment both for the accepting and transferring parties to pay attention.

- *Profiles of impurities on chromatograms of test solutions of samples in the accepting and transferring laboratories.* Guidance ISPE recommends that impurity profiles should be compared in transfer of methods for impurity determination [20]. It is important not only for reliability of method transfer from one laboratory to another one. The comparison of impurity profiles can be used for the search of causes of a negative result of method transfer. For that purpose, if necessary, results of stress tests and drug stability studies are used, a column is cleaned, etc. It is important to establish and eliminate a cause of "excessive" or "missing" peaks and get similar impurity profiles in the transferring and accepting laboratories.
- *Difference in sensitivity of detectors and increased noise of the baseline at the accepting party.* The factors may strongly influence mainly the result of checking of

chromatographic system sensitivity at the accepting laboratory [29]. The attention should be paid on a type of a detector specified in the method. For example, if "UV-detector" is stated in the method, it is better not to use a diode array detector (DAD) as it may have insufficient sensitivity. It is preferable for the transferring laboratory that the method provides signal/noise ratio S/N of the baseline at least 15–20 in solution chromatography to check system sensitivity. It minimizes the risk of insufficient system sensitivity in the accepting laboratory. Due to that, it is for accepting system to provide adequate noise of the baseline.

- *Sample shipment and storage conditions*. Special attention should be paid on shipment conditions, as well as correct storage of samples to be transferred. The author knows the case when contents of impurities significantly increased when the drug sample was shipped for about 2 hours in winter time within a heated car. It was confirmed by the repeated analysis of the returned sample in transferring laboratory.
- *Quality of water, diluents, reagents, reference samples, salts*. The factor may be crucial especially for gradient methods for determination of impurities. Attention is paid that term "water" in compendial monographs with chromatographic methods means specially purified water for chromatography. The use of water with quality grade "purified water" and "distilled water", as well as diluents not intended for chromatography lead to recording of peaks of impurities not typical for a tested sample. Quality of diluents, reference samples and reagents should meet the requirements specified in the method to be transferred. It also refers to salts. An error may be caused by the use of anhydrous salts instead of hydrates or vice versa hydrates instead of anhydrous salts. The use of paired reagents alkyl sulfates instead of alkyl sulfonates, etc. may be crucial.
- *Influence of a long-term degasification of mobile phase while filtered or ultrasonified.* The factor may negatively affect transfer results if mobile phase contains a small amount of a volatile component, for example, acetonitrile. In such cases, from our experience, we recommend that mobile phase should be degasified with degasifiers built in to a chromatograph. Alternatively, due to a partial evaporation of a diluent, retention time of chromatographic peaks and loss of method specificity may change.
- *The use of automatic mixing of eluents in a chromatograph instead of a manual preparation of a mobile phase and visa versa*. The fact may lead to the difference of a ratio between organic component of a mobile phase and water for several percent [30]. It may lead to a significant change of retention time of chromatographic peaks. Therefore the method specified in the method to be transferred should be used in method transfer.
- *Environmental temperature*. It is known that temperature of a chromatographic column, as well as temperature of thermolabile samples influences results of impurity determination [30, 31]. At the same time, not always attention is paid on temperature of a room where chromatographs are located. It should be several grades lower than thermostat and column temperature if column cooling is not provided in a thermostat.
- *Significant difference in dwell volume in gradient elution*. The factor may lead to various retention times of chromatographic peaks, form change and even overlapping of some peaks [32]. Due to that, dwell volume should be determined in gradient elution [18, p. 86], and if necessary, time in gradient program should be recalculated by the certain equation. If dwell volume value is given in the method to be transferred, then time points t_c (min) given in gradient program are recalculated by equation:

$$t_c = t \cdot \frac{D - D_0}{F}, \quad (8)$$

where D – dwell volume, ml; D_0 – dwell volume given in the method to be transferred, ml; F – rate of mobile phase, ml/min [5].

- *Heating of a solution while being ultrasonified.* The factor may serve as a cause of a significant divergence between results of impurity determination in the transferring and accepting laboratories. Therefore when solutions of test and reference samples are ultrasonified, water should be cooled in ultrasonic bath. For that, it is better to use a circulation

thermostat with assigned temperature of cooling water.

- *Sorption of substances to be determined on a filter, glass and other surfaces*. To minimize a risk of a negative effect of the factor in the accepting laboratory, only such filters and glassware specified in the method to be transferred should be used. As for biological molecules, capillary tubes and chromatograph nodes from PEEK material (polyether ether ketone) can be required. Issues related to sorption of drug substances on glass and plastic are reviewed in [33–35].

In practice, a negative influence of other factors may occur in practice in method transfer. You may search, if necessary, in recommendations from [18, 29–31, 36–38], as well as, in the internet by a key word Troubleshooting.

- *In method transfer, determinations of impurities for a drug with several dosages analyzed with the same method, the least dosage is used*. Such approach is often used in companies. However it may be related to a risk for the accepting party. Due to that, you should be sure that additional peaks should be absent on chromatograms of placebo solution in higher dosages compared to the least dosage.

What is more preferable in method transfer: comparative testing of samples or method validation?

There is no a definite answer to the question. From a theoretical point of view, a partial and full method validation has a certain advantage. As results of a comparative testing of samples may depend on properties of samples to be transferred and impurities contained (as stated above) but on the method itself. The use of generally adopted acceptance criteria is an additional advantage of method validation. Moreover, in validation of a method to be transferred, values of correction coefficients (F) for identified impurities are checked and sometimes specified. The author knows the case when a value of relative sensitivity coefficient RRF = 1/F was erroneously used in the numerator of the calculation equation instead of a correction coefficient F in the method transferred from a foreign company.

On the other hand, a comparative testing of samples has an important advantage. It is a simpler testing of a method to be transferred and gives opportunity "to check understandability of method narrative for a common executor", as well as, to determine "narrow" aspects of a method (they should be considered in routine analyses). A result of comparative testing may be important not only for the accepting party but also for the transferring party. If necessary, the transferring party has opportunity to clarify a method. Due to that, as well due to simplicity and clarity, a comparative testing of samples is significantly more widespread than validation of a method to be transferred.

CONCLUSION

The data and recommendations given above are important for the increase of reliability of transfer of methods for impurity determination. They may be used for justification of selection of method transfer for procedures, acceptability criteria and evaluation of transfer results.

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