Analytical method transfer

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Near-infrared spectroscopy (NIRS) is a widely used analytical technique for qualitative and quantitative analysis of various products in research and industrial applications. Because of different reasons it might be necessary to transfer analytical methods from one NIR analyzer to another one. This white paper summarizes the workflow of such method transfer.

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Introduction

The transfer of analytical methods enables one analytical laboratory, a so called receiving laboratory, to use the method developed in another laboratory, a so called transferring laboratory [1]. The successful method transfer provides several benefits for the customer such as:

Cost- and time savings

Development of an analytical method can be a very time consuming procedure and therefore also cost intensive. When customers decide to purchase a second analyzer for the same application, two options are possible (**Figure 1**). Firstly, the method can be redeveloped from scratch on the new analyzer, which means that the time and cost intensive procedure has to be repeated. On the other hand, customers can simply transfer the method from the first analyzer. In an ideal case this procedure can be performed without any additional adjustments and customers can immediately start to work on the new instrument.

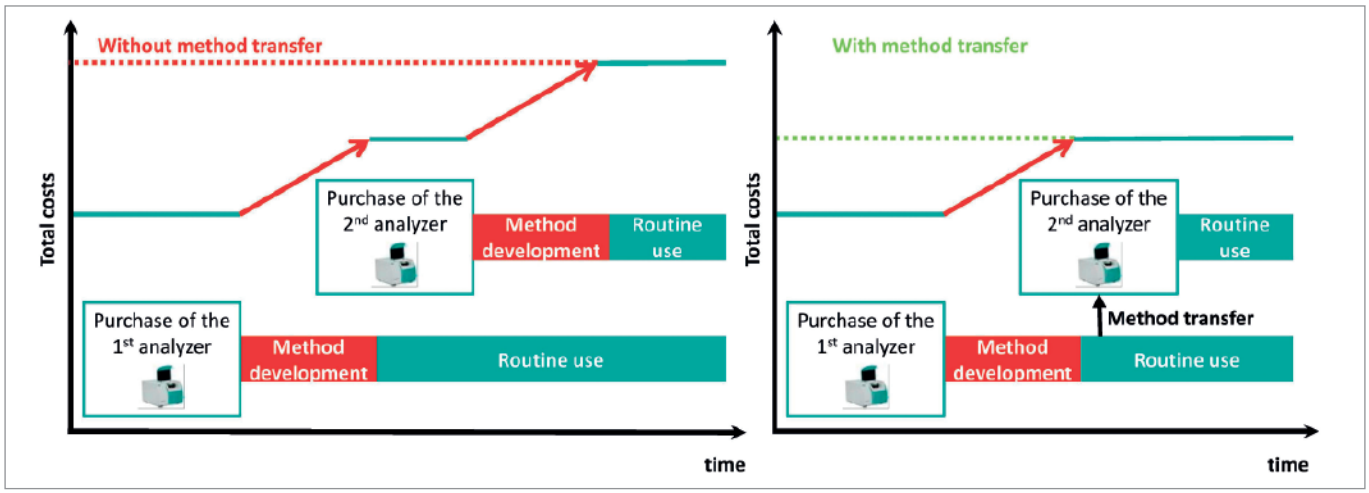

Figure 1. Costs for the method development with and without method transfer.

Harmonization

An effective analytical method transfer enables synchronization of operating procedures all over the world and managing multiple calibrations across multiple sites. This synchronizes and simplifies quality control (QC) at different production sites inside the same company (**Figure 2**).

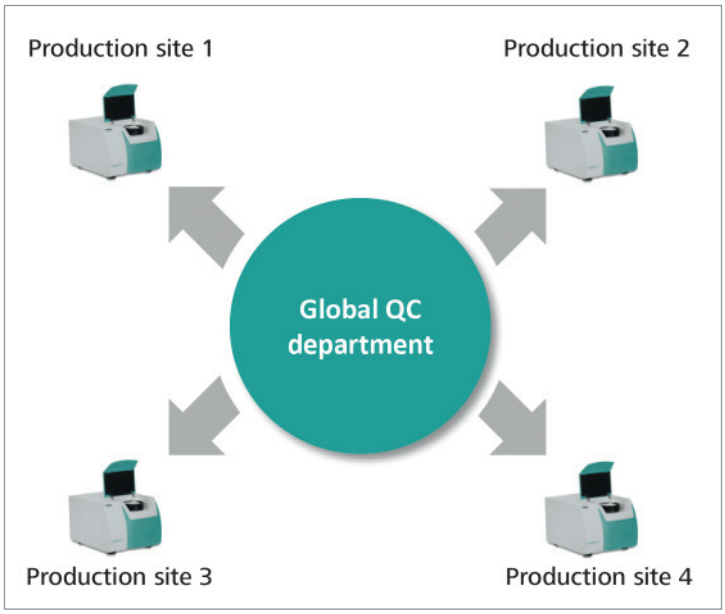

Figure 2. Harmonization of QC procedures.

Improvement of analytical performance

An effective method transfer enables the transition from old instruments or instruments provided by other vendors (**Figure 3**). For example, new instruments are developed using technical innovations. They usually have improved technical specifications. Additionally, another vendor can offer additional services such as superior support and/or quality or provide an analyzer with improved technical specifications. Both examples result in the increase of the analytical performance and significant improvement of the customer's process.

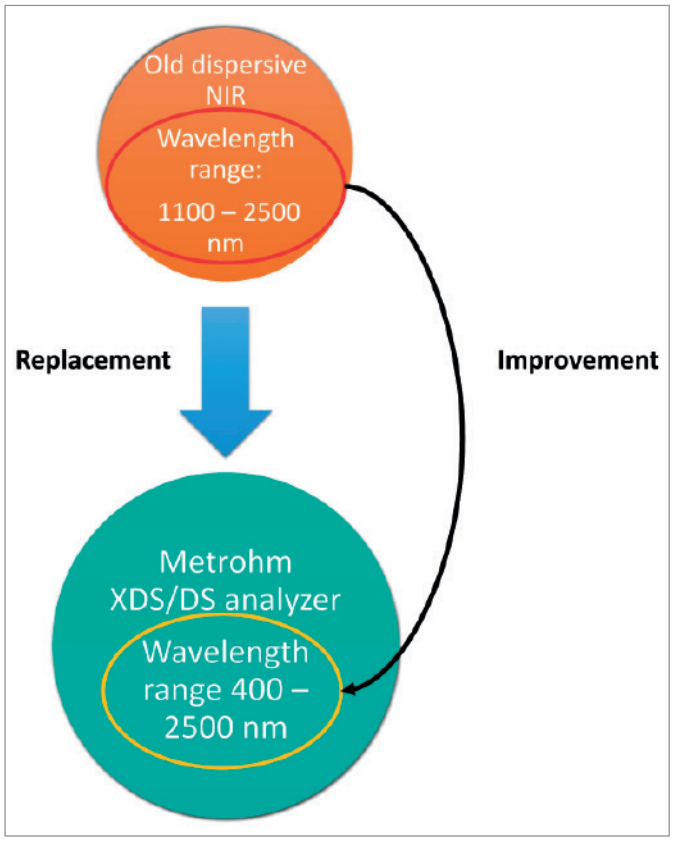

Figure 3. Improvement of the analytical performance.

Quite often it is not possible to transfer the analytical procedures from the transferring laboratory directly to the receiving laboratory without any additional adjustments. The necessity of such updates can be explained by technical differences between involved analyzers such as detector sensitivity or wavelength range. In this case, the method developed on the source instrument should be corrected so it can be utilized with the target instrument. This is called standardization. The extent of the standardization can be minimized, when the methods that need to be transferred are robust and the source and target instrument are calibrated in a similar way e.g. using same type of calibration standards. This is for example the case for dispersive NIR instruments provided by Metrohm.

All types of the analytical method transfer have five common steps: preparation, method transfer itself, validation, method update, and finally routine application (**Figure 4**). During the preparation phase the scope of transfer and the transfer procedure have to be defined. The transfer itself can be a twostep procedure. In the first step it may be necessary to standardize both instruments. This standardization has to be applied on the calibration data from the source instrument in order to use the calibration data on the target instrument. The transferred methods need to be validated using an independent sample set. Based on the validation results it may be necessary to adjust the method before using it in routine analysis.

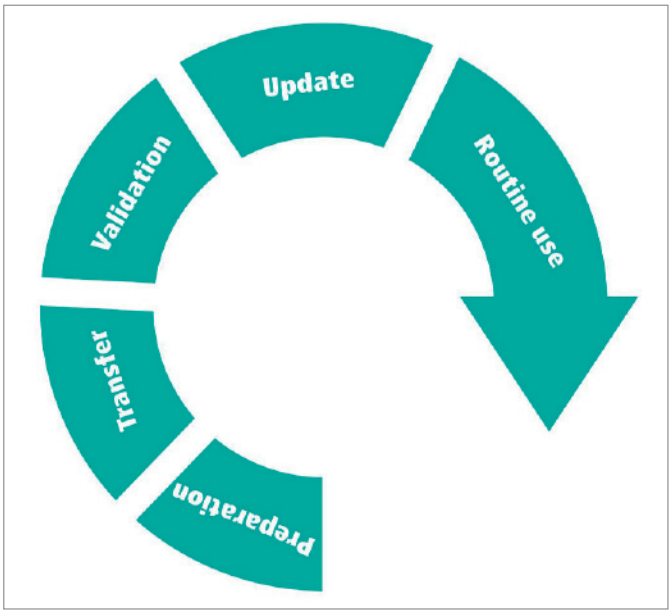

Figure 4. General workflow of the analytical method transfer.

However, these steps differ for various types of the involved source and target instruments. The difference can be easily explained by a comparison between purchasing of a new instrument with the purchase of a new car. The adjustment is minimal when buying the same car model again. The same model albeit a newer edition is usually built using technical innovations and provides new features. Therefore it is slightly different than the previous model and the driver needs time to get used to it. Switching to a different car manufacturer requires more time and efforts for the driver to get used to it.

Finally, driving of an ambulance is more complex than driving of an ordinary car because of additional regulations. The various types of the method transfer in analytical chemistry are very similar to this example. In general the following types of method transfer exist in the area of spectroscopy:

- The method transfer between identical instruments, e.g., the same instrument model is easy to accomplish.
- The method transfer between similar instruments, e.g., transition from the previous model to a new one can require additional efforts.
- The method transfer between instruments provided by different vendors, e.g., from FT-NIR to dispersive NIR instruments is more complex and requires additional measurements.
- The transfer of analytical procedures in regulated environments such as the pharmaceutical industry is a special case of method transfer due to specific regulations of this industry field.

These four types of method transfer are briefly summarized in the present white paper together with different challenges, benefits, and recommended procedures.

Transfer between identical instruments

This is the simplest type of analytical method transfer. An important requirement is that both analyzers are calibrated in the same way, which is the case for dispersive NIR instruments provided by Metrohm. They also should be operated under the similar conditions e.g. vials with the same diameter should be used for liquid samples. Here, the analytical method can just be copied to the new analyzer and the operator can immediately start using it on the new system.

Example of such a transfer is summarized in **Application Note AN-NIR-011 Calibration model transfer of caffeine on the NIRS XDS Rapid Content Analyzer [2]**. In this application, the method for caffeine determination was transferred from one analyzer to three similar analyzers. During the validation phase, it was demonstrated that the standard error of prediction for all new analyzers after the method transfer was in the same range as the error of prediction for the original analyzer. Therefore, it was not necessary to update the models and the customer could immediately start to work with the new analyzers. This simplification of the analytical method transfer can be explained by the excellent quality of dispersive instruments and the dedicated procedure for the standardization implemented for all Metrohm NIR instruments.

This advantage of dispersive NIR instruments enables unique possibilities for further improvement of the performance, harmonization, and costsavings for the customer when performing an analytical method transfer.

Previously, when operating multiple production sites with local quality control laboratories, one had to establish separate QC procedures and hire and train an analytical chemist and QC manager in each production site.

Nowadays, quality control using NIR technology can be simplified, when the customer uses dispersive Vis-NIR technology and dedicated networking software like Vision Air Server (**Figure 5**). In this case, the customer can set up a global expert team located at his headquarter, which can consist of a global QC manager and an analytical chemist and involve an IT manager. This global expert team can establish operating procedures and transfer them to each connected single plant. This means that all operating procedures can be synchronized between different production sites. Furthermore, with Vision Air Server it is not only possible to synchronize all operating procedures but also to store all results measured at each plant centrally at the company's headquarter. The global expert team can monitor all Metrohm NIR analyzers all over the world. All out-of-spec (OOS) or out-of-trend (OOT) situations are automatically reported to the global expert team. In case of OOS or OOT situations the global expert team can immediately intervene and solve problems on the spot before they become critical. Without this possibility the headquarters may only be informed about problems at other production sites when they escalate, e.g., when the corresponding plant receives a warning letter from regulatory body or when the product recall is reported in newspapers.

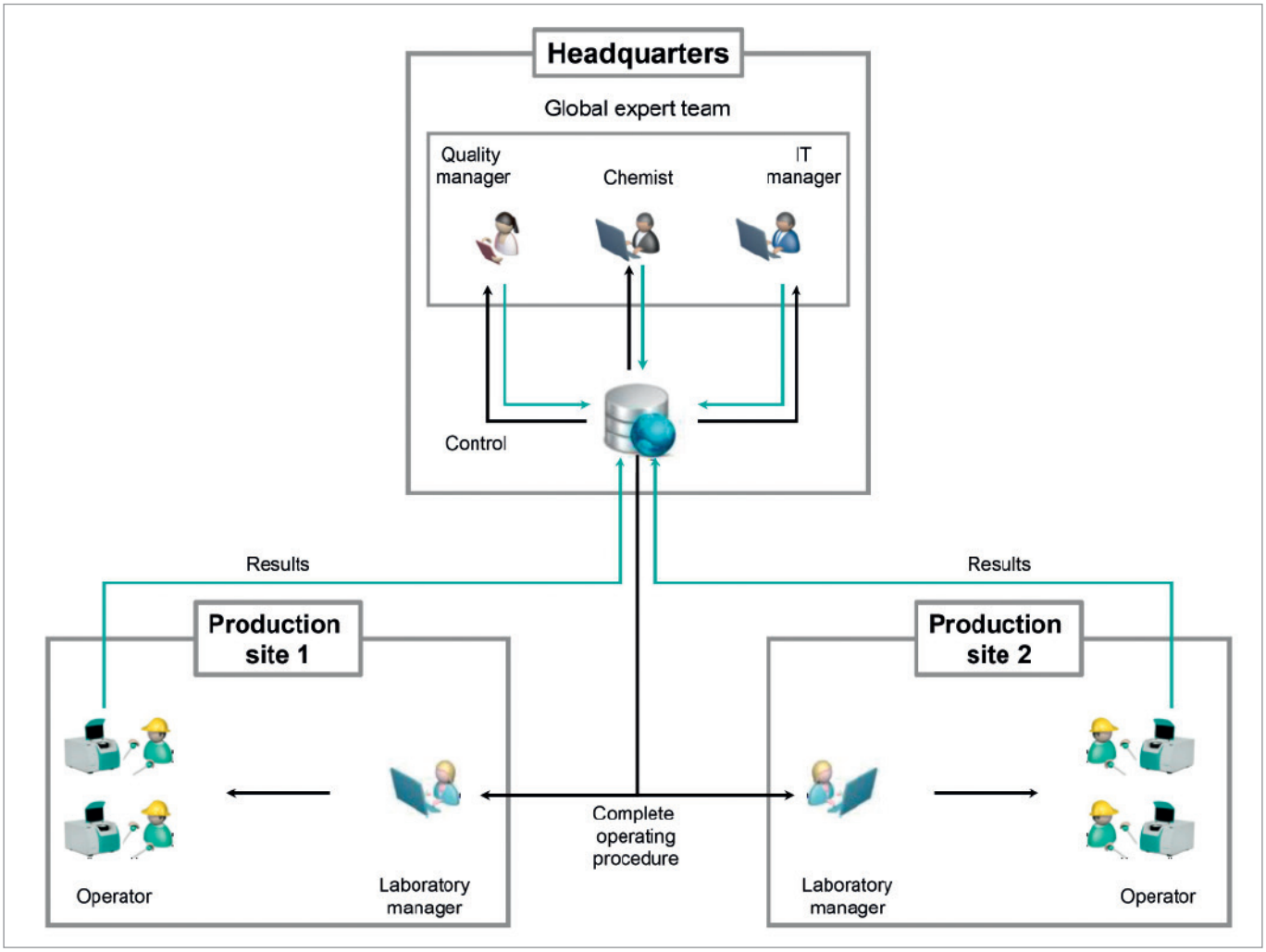

Figure 5. Schematic workflow of the harmonization of the global quality control using Vision Air Sever.

Transfer between similar instruments

Previous model to new model

This type of the method transfer is also quite often straightforward to accomplish but it requires some additional steps. Older and newer analyzers are based on the same technology but the newer one has improved technical specifications such as higher resolution or an extended/reduced wavelength range. In this case, the spectra of the old instrument can be easily converted in order to be utilized with the new analyzer. This conversion is usually often straightforward using the provided software, e.g., Metrohm Vision software for NIR spectrometers, which enables the conversion of data from older System II analyzers in order for such data to be used on modern Metrohm NIR analyzers. Afterwards the method from the older model needs to be validated on the new one. In case of qualitative methods it might be necessary to add some spectra collected on the newer analyzer to the method. Quantitative applications can be easily updated using a simple slope/bias adjustment supported by the software. Here, it is recommended to use a validation set, which spans 90–95% of the initial calibration range.

One important remark should be made regarding the analytical performance of the transferred method. If the purpose of the new analyzer is not only a replacement of the old hardware but also an improvement of the analytical performance,

then it is recommended to redevelop the analytical method on the new analyzer. Obviously, it is not realistic to expect the same driving performance when using the engine of 100 year old car in a new car model. The same is true for NIR methods. As mentioned before, new analyzers have improved technical specifications, which go in hand with an enhanced analytical performance. Redevelopment of the analytical methods using these benefits can result in significant improvement of the analytical figures of merit as it was demonstrated in the **Application Note AN-NIR-028 «Data and method transfer from System II analyzer to Metrohm NIRS XDS or DS2500 analyzer».** A method transferred from the old analyzer can be used as an intermediate solution. The customer can avoid the downtime of the QC lab using the transferred method and collect enough spectra for the development of a new NIR method with improved analytical performance on his latest analyzer.

Laboratory application to the process analysis

Quite often, the implementation of NIR technology starts with its application in the QC lab or atline close to the production process. After a certain time the customer may become excited about the benefits of NIR technology, such as significant cost- and time-savings and plans the implementation of NIR instruments inline or online throughout his production. Reasons for this can be the wish to improve the production process or improving product quality by implementing the quality by design principles. Such an implementation of NIR process applications is accompanied by the request to transfer the previously developed atline or offline NIR methods to the process NIR instrument in order to reduce the time needed for the method development.

Such transfer from a laboratory application to a process application is more challenging than the previously described examples. The reason is the difference in the measurement conditions between both analyzers. E.g., the temperature of the sample in a reactor is usually much higher. The sample introduction in the process can be affected by bubbles or sample flow. Process samples can have additives like, e.g., catalyst.

However, such a method transfer may still be possible and it is supported by a local Metrohm agency. Here, it is essential to validate the method and to perform a slope/bias adjustment as described before. Because of the mentioned differences it is normal that the standard error of prediction increases, when transferring the method from a laboratory NIR to a process NIR. In order to minimize the error of prediction it is recommended to transfer methods, where the measurement conditions in the laboratory are as close as possible to the final process conditions, e.g., the sample temperature should be identical.

Transfer between instruments from different vendors

An NIR user may decide to switch to an instrument from a different manufacturer with completely different technology. Reasons for such a change range from insufficient performance of the old hardware to dissatisfaction with the support and service of the former supplier. Such a transition is usually accompanied by the customer's request to transfer the data from the old analyzer to the new one to avoid the cumbersome and time-consuming method development from scratch.

Such a transfer is the most challenging type and requires some additional steps such as measurement of additional samples on both analyzers (**Figure 6**, **[3]**). Usually, it is recommended to use 15–30 representative and stable calibration samples. The spectra of these samples are used for the calculation of a so called transfer function. Afterwards this transfer function is applied on the calibration data of the source analyzer in order to use it on the target instrument. After the successful validation, the customer can start to use the transferred analytical methods. This process is supported by a local Metrohm agency and demonstrated in detail in the **Application Note AN-NIR-043 Analytical data transfer between a Fourier transform and a dispersive NIR instrument [4]**.

The analytical performance of the transferred method should be mentioned in detail. Firstly, the error of prediction after the method transfer will be higher because of two reasons. The method from the source instrument is characterized by its error.

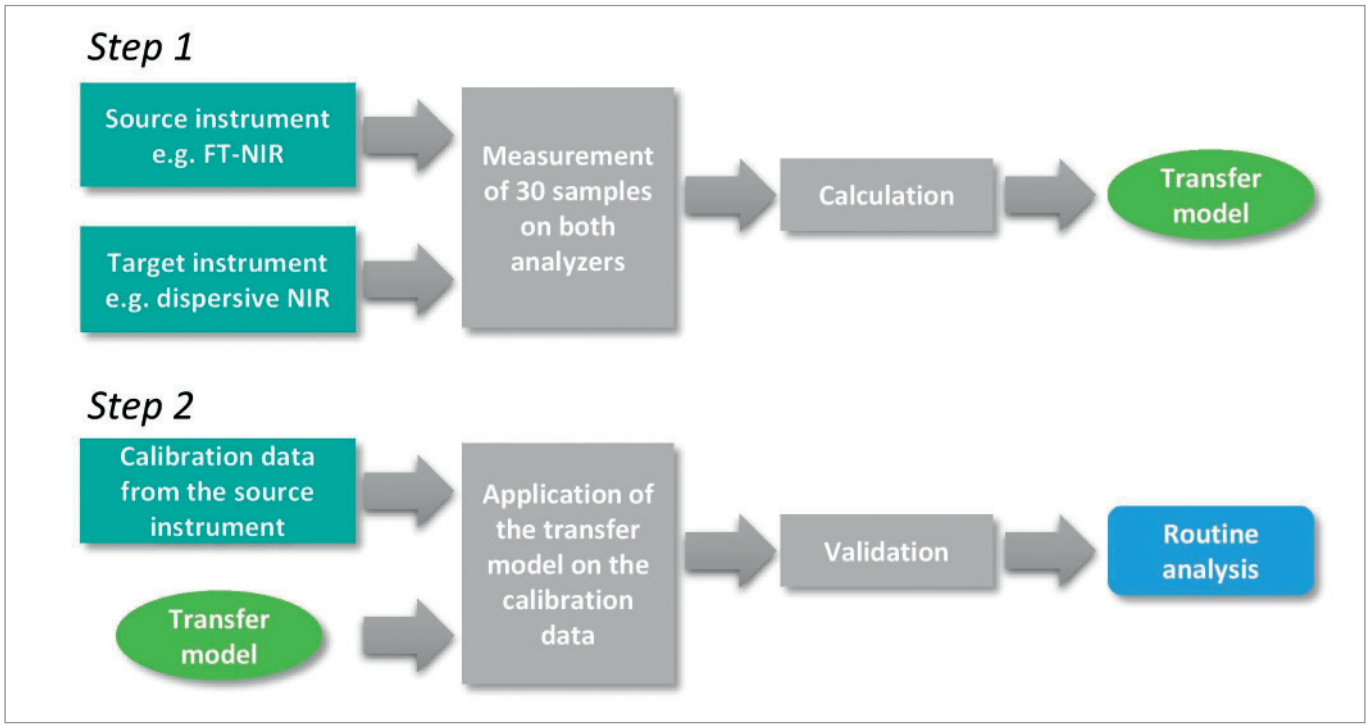

Figure 6. Schematic workflow for the method transfer between instruments from different vendors e.g. from FT-NIR to a dispersive.

The standardization introduces an additional error. The combination of both errors during transfer increases the total error estimated using the transferred method on the target instrument. This is the law of nature, a so called Gaussian law of error propagation and there is no possibility to overcome it.

Secondly, the transfer does not eliminate all problems of the original method. For example, when the original method was developed on a NIR analyzer then the analytical figures of merit are affected by a higher noise and lower signal-to-noise ratio or other characteristics of the FT-NIR technology (**Figure 7**, for further details see reference **[5]** and references there-in). The transfer of these spectra to a dispersive NIR instrument characterized by its very low noise level and enhanced signal-to-noise ratio does not eliminate the original problem. The high noise of the original FT-NIR spectra is just transferred to a dispersive system with a low noise level and it has still an impact on the analytical performance. In such a case, it is recommended to use the transferred methods only as an intermediate solution in order to avoid the downtime of the laboratory, collect enough spectra on the dispersive NIR instrument with enhanced noise level, and develop a new method with improved analytical performance.

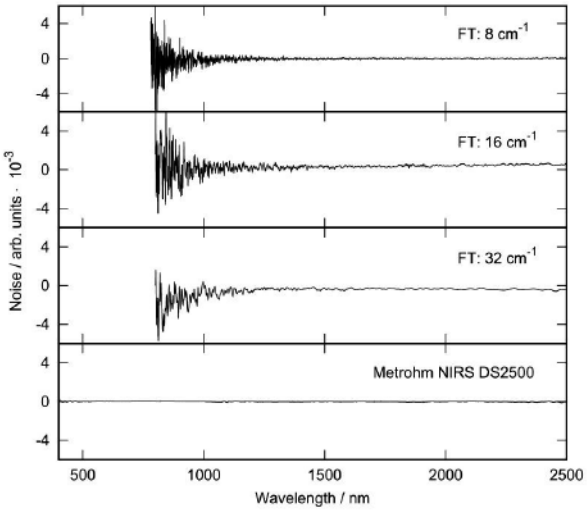

Figure 7. Noise spectra acquired with the Metrohm NIRS DS2500 in a spectral range of 400–2 500 nm and an FT-NIR instrument with a spectral range of 800–2 500 nm in reflection mode **[5]**.

By the way, the transfer the other way around from a dispersive NIR to a FT-NIR leads usually to additional disadvantages for the customer. Here, the noise of the FT-NIR is added to low noise dispersive spectra, which has a negative impact on the analytical performance. Additionally, the spectral range below 800 nm is usually not accessible when using FT-NIR due to physical limitations of this technology. After the method transfer the visible region is not available anymore and the customer has to buy an additional UV/VIS instrument if he would still like to cover this range.

Transfer in the pharmaceutical industry

The pharmaceutical industry is unique with its extensive regulations such as the United States Pharmacopoeia **[6]** or European Pharmacopoeia **[7]**. In this area, the whole process is quite often called transfer of analytical procedures (TAP). In contrast to the previously described transfer the source unit is responsible for providing not only the analytical method, but also the reference standards, the validation reports, and any additional documentation required (**Figure 8**, **[1]**). It is also responsible for the training and assistance to the receiving unit.

Prior to the transfer, a preapproved protocol between both receiving and source laboratories should be discussed, agreed, and documented. All relevant information like scope, objective, responsibilities of all involved laborator ies, analytical procedure, used materials and instruments, experimental description of the transfer as well as acceptance criteria for all used tests and methods should be documented in this protocol. This process is usually coordinated by a customer's quality assurance department.

Different approaches are mentioned to be suitable for the transfer of analytical procedures, namely comparative testing, covalidation, revalidation and transfer waiver, which is possible under specific conditions. The selected approach should be documented in the previously described protocol.

A part of the TAP is the transfer of the analytical model from the source NIR instrument to the target instrument. There is no detailed information about the procedure of the model transfer in pharmacopoeia chapters for NIR spectroscopy **[8, 9]**. This allows for the possibility to use various mathematical and statistical methods for the model transfer. However, it is stated that «procedures and criteria must be applied to demonstrate that the model remains valid» after transfer **[8, 9]**. This means that the transferred analytical model must be validated and verified, e.g., according to USP chapter <1225> «Validation of compendial procedures» and USP chapter <1226> «Verification of compendial procedures» **[10, 11]**. Furthermore, it may be mandatory to perform validation using ICH Q2 guidelines, which requires the estimation of additional analytical figures of merit **[12]**.

Important for the successful transfer of the analytical procedures is also the final report, which summarizes all results, deviations and adjustments. Furthermore, it should be documented, if the transferred procedure meets the acceptance criteria defined in the preapproved protocol. The transferred procedure can be used for a final routine application only when it fulfills these criteria. Otherwise, the reasons of the deviation must be investigated and the involved laboratories have to adopt effective remedial steps.

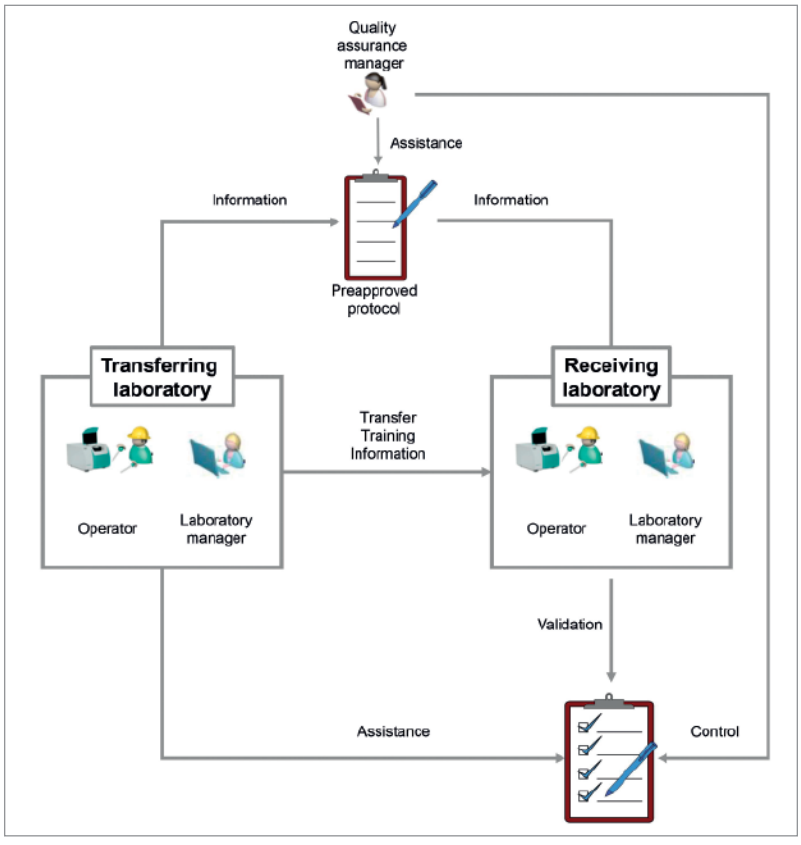

Figure 8. Transfer of analytical procedures in pharmaceutical industry.

Summary

The present white paper describes different types of the analytical method transfer. In the simplest case, when using similar well calibrated analyzers like Metrohm NIR analyzers, the customer can simply copy the method from one instrument to another one. In combination with the Metrohm Networking Software Vision Air this approach enables unique possibility to synchronize and monitor the quality control all over the production sites of the company.

The analytical method transfer from old analyzers or from various vendors is more complex and requires additional steps, and can be supported by a local Metrohm representative. For both cases the local Metrohm agency can provide further information and support.

Furthermore, the difference between the transfer of the analytical models and the transfer of the analytical procedures in a pharmaceutical environment was pointed out. As mentioned before, a local Metrohm representative can provide support with the transfer of the models. However, the transfer of the complete analytical procedure lies in this case in responsibility of the customer's quality assurance department.

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