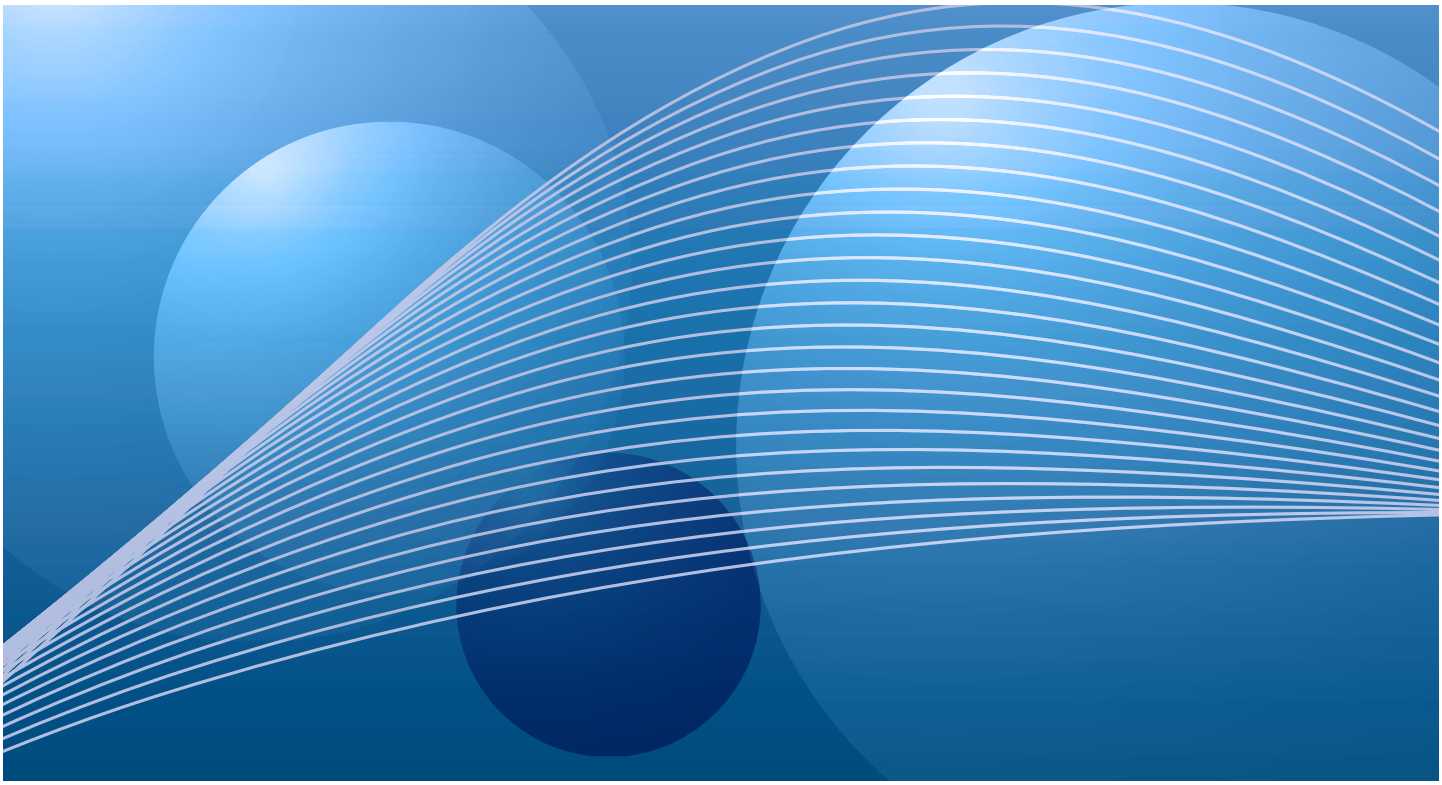

White Paper

Challenges of Analytical Method Transfer in the Pharmaceutical Industry

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Introduction

The development and validation of suitable analytical methods is a critical part of the overall drug-development life-cycle. For the majority of products, particularly those that are clinically successful, the transfer of the analytical method between laboratories will be required. This process is designed to verify that a given laboratory is capable of performing a test method for its intended purpose. This can be performed either internally (at the same company), or, with the on-going increasing trend in outsourcing, to an external Contract Research or Development organisation (CRO or CDO).

Very often, the analytical method transfer can be underestimated in terms of its relative importance to the continued success of a drug-development program. The execution of the process needs to be very carefully planned, and a full review of all aspects of the method history (including the original development and validation) and any previous issues that may have been encountered. This White Paper aims to outline the key considerations, components and expected outputs to ensure a successful transfer and continued use of the analytical method for routine testing.

Method Transfer Team

Prior to initiation of any other activities, a team should be formed to allow key responsibilities to be assigned, ensuring that all areas of the transfer are supported by individuals with appropriate technical and regulatory knowledge. Often, there can be a tendency to involve too many individuals; this can often be very disruptive and ultimately slow down the transfer process. Careful selection should be made at the outset and include only individuals who have the appropriate knowledge and experience for the method(s) being assessed.

Figure 1 outlines the key milestones to be included when conducting the method transfer:

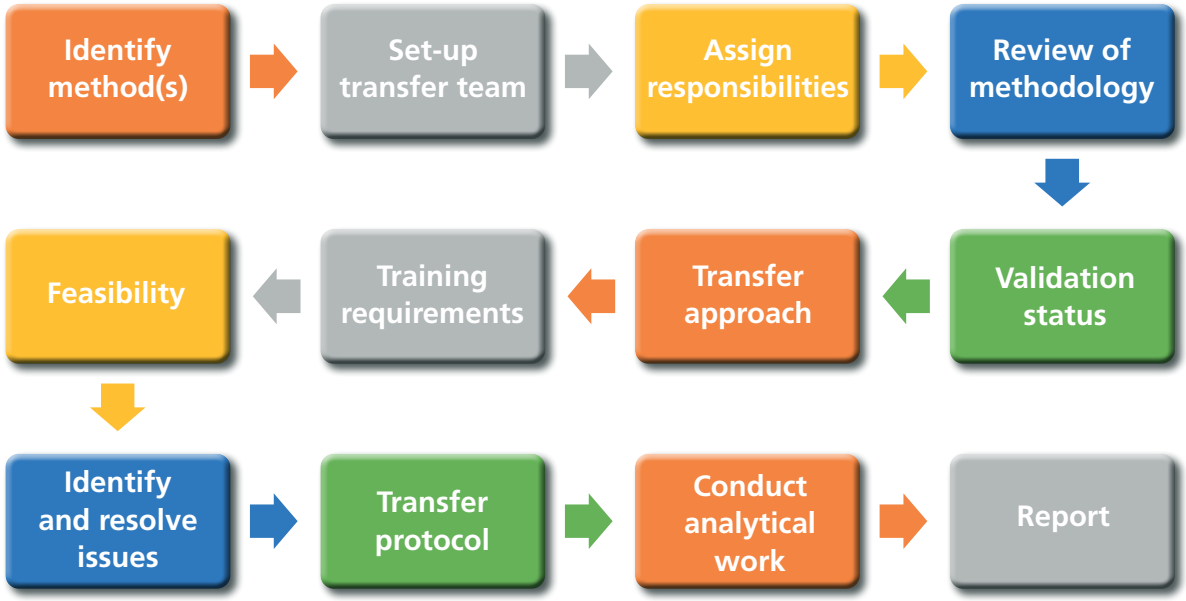


Figure 1: Method transfer process

Each team member should be assigned a specific role; this ensures that there are clear lines of responsibility, ensuring that the process can be executed as efficiently as possible. Although there may be some variation, some key functions should be assigned:

1. Project Lead

This role is pivotal and will co-ordinate the entire transfer process. Typical functions include organising/chairing meetings (including frequency and meeting format), assigning responsibilities and overall management of the project timeline. Essentially, this individual must critically monitor and lead the team to ensure that any issues are effectively dealt with by the appropriate members and an effective resolution can be sought in order to keep the project on track.

2. Technical Lead (originating laboratory)

In order to avoid any unwanted 'surprises' further down the line, the Technical Lead is responsible for providing the historical background and documentation pertaining to the method(s) being transferred. Very often, there are many years of data that will prove valuable when assessing a method. It should be borne in mind that the entire purpose of the analytical method transfer is to have a validated method to transfer. Methods are often presented for transfer that may have been validated previously to very different regulatory standards. This would ultimately need to be assessed against current ICH guidelines.

For any method, a comprehensive 'gap' analysis should be undertaken to identify any parameters that would require additional validation as part of the transfer process. For older methods, it may be recommended that a full re-validation is performed (often preceded by method development) to align the procedure with current regulatory guidelines.

3. Technical Lead (receiving laboratory)

The function of this role is in co-ordinating the lab activities at the receiving site. This includes a number of key aspects:

- Review of documentation
- Co-ordination of trials/training
- Preparation of protocols/reports
- Investigation/resolution of technical issues

4. Quality Assurance Representative (receiving laboratory)

In many respects, this function is self-explanatory, but this individual is responsible for ensuring that the method transfer activities are performed according to current regulatory guidelines as well as aligned with in-house SOPs. They would also be expected to review and/or approve protocols, reports and deviations.

Identify Method(s)

This may seem quite obvious, but it is important to ensure that a full evaluation of all required methods is drawn up. It is far more efficient to conduct multiple transfers synergistically, ideally covering multiple methods under a single protocol. This would require full discussion within the transfer team, with particular emphasis upon scrutiny of all the method files within the current regulatory submission.

The originating lab must provide a package of documentation prior to starting any feasibility or transfer work. The following should be supplied/requested:

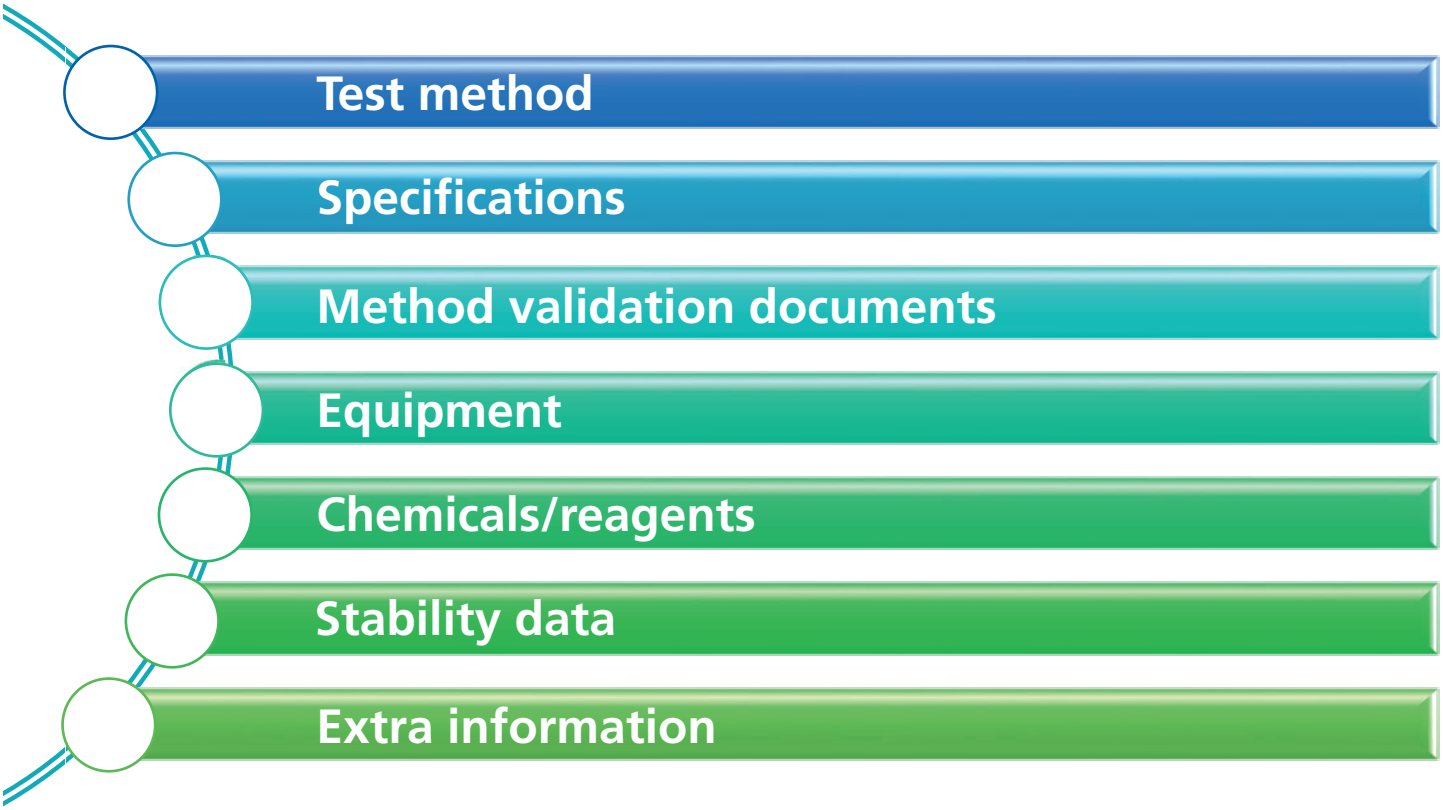


Figure 2: Method transfer requirements

The body of information above will allow for a full evaluation of the overall history of the methods and the ability of the receiving laboratory to undertake the transfer.

Gap Analysis

In terms the current method, it should be fully reviewed to ensure that it is identical to the registered test method, and that any claims made in the method are supported by the method validation.

The method should be clear (i.e. easy to follow), unambiguous and free from any errors. If the method is in a different language, ensure that this is fully translated (including any nuances) by a specialist translator prior to use.

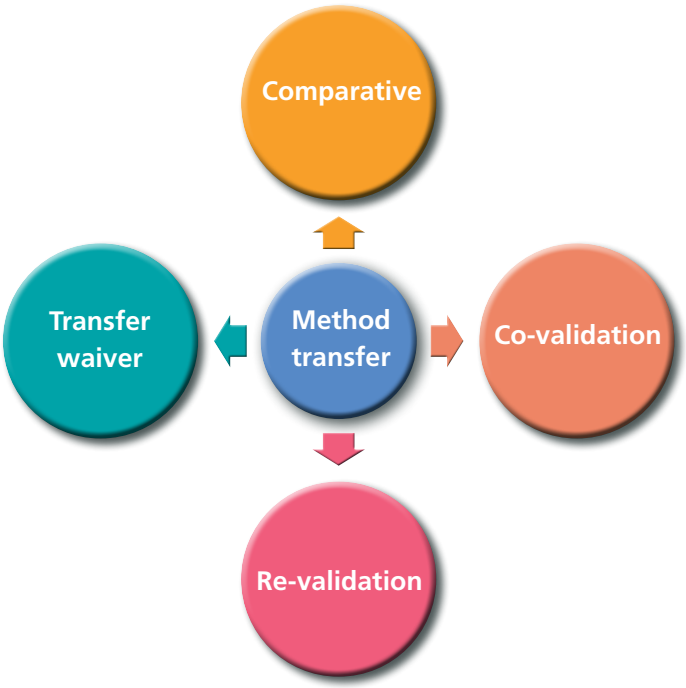
Other aspects to verify:

1. Validation was performed in accordance with current ICH guidelines
2. Validation was performed in accordance with the current procedure of the receiving laboratory
3. Validation design covers the intended use of the method (e.g. release/stability/in-process testing etc.)
4. Results obtained met the acceptance criteria
5. If non-compliances occurred, were these adequately investigated and suitable remedial action taken

Aside from the methods, it is also important to verify that all instrumentation, chemicals and other specific consumables, are available at the receiving laboratory in the time-frame needed to perform the method transfer.

Method Transfer Strategies

When undertaking analytical method transfer, it is important to base the approach on the stage of development. As would be expected, the later the stage in the development life-cycle, the more stringent the requirements. Therefore, it is recommended that an assessment is undertaken to identify and define the risk level specific to a given method. Additionally, in determining the transfer strategy to be used, an evaluation should be performed with regards to (1) nature of the method, (2) its validated status, (3) the intended product and (4) experience of the receiving laboratory. Depending upon the outcome of these evaluations, the approach to the method transfer may vary. Also, the specific use of the method (e.g. release, stability, in-process etc.) should be fully considered. This should be agreed as a team and then fully documented and approved by all team members. The various strategies are outlined below:



The type of method, experimental design and data analysis should be tailored to each specific situation to allow regulatory expectations to be satisfied. A method transfer can be greatly simplified if, for example, the receiving lab has experience in the execution of a similar method, different strengths or dosage forms of the same product, compendia methods or a product that is in a very early stage of development (i.e. pre-clinical).

The likelihood of a successful outcome for the method transfer is far greater with increased understanding of the method(s).

1. Comparative Testing

This represents the most commonly used approach for method transfer. This option involves the testing of the same sample at both the originating and receiving laboratory followed by a comparison of the results. All work is performed against a pre-approved protocol, complete with pre-determined acceptance criteria. It is possible to use comparative testing in conjunction with other post-approval scenarios involving additional manufacturing sites or contract laboratories. Broadly speaking, comparative testing is most frequently used for later stage methods and the transfer of more complex methods.

2. Co-validation

As discussed earlier, a validated method is normally a pre-requisite for a method transfer. However, an alternative approach to the comparative transfer is to involve the receiving laboratory from the start in the actual validation of the method being transferred. Once the process is completed, the laboratory is deemed qualified to perform the analytical method for release testing. In order to use this as a transfer option, the receiving laboratory must be involved in identifying the intermediate precision validation parameters to be evaluated together with the experimental design. By the very virtue of submitting data from all laboratories involved in the study, the validation report can be accepted as proof of a successful transfer.

3. Re-validation

Consider the scenario where the analytical laboratory that originally developed a test method is no longer in business. In this scenario, comparative or co-validation approaches are not an option since they would both require data generated by both the originating and receiving laboratory. If the method had previously been validated at the source lab, then some gap analysis would need to be performed in line with our earlier discussions. Once this has been performed, any parameters that were not included within the initial validation should be completed, and then the transfer would involve a re-validation of parameters deemed to be critical to the method. The decision as to which of the parameters to re-assess must be based upon the entire body of data pertaining to the method, product and the type of testing in question. This should be discussed and agreed by the entire team.

Method Transfer Waiver

There are occasions whereby a formal method transfer may not be required. Typical situations where this may be applicable are:

Compendia methods

1. If the receiving laboratory is already testing the product and is completely familiar with the procedure.
2. Where a method or procedure for a comparable dosage form is already in place at the receiving laboratory.
3. If the analytical method (or one very similar) is already in use.
4. Where an existing method has been modified very slightly and the modification does not impact upon its validation status.
5. If personnel accompany the transfer of the method from the originating to the receiving laboratory.

If a transfer waiver is deemed appropriate, the receiving laboratory can use the method without generating any comparative data. This must all be accompanied by a fully documented justification for the waiver.

There are many aspects needed in order to execute a successful method transfer. As with method validation, documentation is absolutely pivotal. This process commences with a protocol and concludes with a transfer report. All activities must be fully detailed and traceable for compliance purposes.

Prior to proceeding with the transfer, a protocol must be prepared. This will be discussed later in this paper.

The process of training needs to be established. Very often, this can be over-looked as it is assumed that any analyst can follow a given method. However, there are often idiosyncrasies that are not detailed in the method and only known by the originating laboratory. Therefore, it is crucial that these potential issues are captured as early as possible in the process so as they can be ironed out and any method updates executed accordingly. In light of this, method feasibility is a key part of the overall method transfer strategy and should be given sufficient time and resource to complete.

Different approaches to training:

- Receiving laboratory trial (no hands-on involvement)
- Method training at the receiving laboratory
- Method training at the sending laboratory

The approach taken is ultimately dependent upon the complexities of the specific method and the experience of the receiving laboratory. No matter which of the above is adopted, all of the training needs to be documented according to GMP requirements.

Method Issues

There are occasions where, despite following a logical, structured approach as outlined in this paper, methods do not perform as well in the receiving laboratory. One of the most common areas for problems are associated with test methods; this generally arises from a lack of detail within the document, leading ambiguity due to scope for interpretation by the user. It is therefore fundamental to the success of the transfer that communication between sending and receiving lab is open and regular. Don't be afraid to sought as much clarification as needed regarding the test method, but always bear in mind that if too many questions need to asked, the method may need to be re-written to provide additional clarity. This should generally be evaluated by performing a method feasibility ahead of the transfer. Don't fall into the trap of transferring a sub-standard method; this will ultimately cause issues further down the line, costing time and money.

Transfer Protocol

As well as considering all of the previous discussion, one of the additional key criteria in a successful method transfer is the protocol. This should describe the scope and objective of the transfer, responsibilities across the transfer sites, list of methods, and justification for any methods excluded from the transfer. It should also include a list of materials and samples to be used for the transfer.

Sample Considerations

The samples to be used for the transfer should be fully considered and justified; these should be representative of materials that are to be tested in the future, but must not be from a current batch. In order to challenge the extraction, ideally the sample should be suitably aged, and available in a sufficient quantity to allow the transfer to be fully executed with an overage in the case that any re-testing is required. The sample should be identical for both laboratories, and testing performed within as short a period as possible to prevent any changes in results due to stability issues occurring, which would potentially lead to results failing to meet the acceptance criteria; obviously, stability of the samples is key when stipulating a testing window, but generally, a period of 30 days from protocol approval would be an acceptable approach. It should be borne in mind that the purpose of the method transfer process is to establish and verify method performance within different laboratories and not changes in samples. Copies of Certificates of Analysis for samples and reference standards should also be included in the transfer protocol (where appropriate).

Instrumentation and accompanying parameters should also be described. Ideally, both laboratories would be using the same instrumentation, although in reality, this isn't always possible. In such circumstance, it is prudent for the originating laboratory to consider running on the instrument common to the receiving laboratory; this will allow early evaluation of any potential issues and ensure these are resolved well ahead of the planned transfer.

Execution of the Method Transfer

Just prior to conducting the transfer, the team should meet to evaluate the feasibility work and ensure that all of the necessary paperwork has been completed at each of the respective sites. Any gap analysis should also be complete and provide a solid foundation upon which to undertake the transfer. As mentioned previously, there should be good control of the testing window between the two laboratories.

One of the worst possible (avoidable) outcomes would be failure of the transfer due to stability of the sample; if testing of the sample at the two laboratories was to occur too far apart, the results could well be impacted by degradation of the sample. It is therefore generally recommended that samples are tested within 30 days (although this would be assessed on a case-by case basis). In the case of related substance methods, it is advisable to include a placebo solution together with individual impurity retention time markers, even though this may not be required by the method; this can really assist with peak tracking and evaluation of any method issues. The sending laboratory should also supply all relevant chromatograms that have been appropriately integrated to ensure that consistent peak integration is performed by both laboratories, thereby removing this as a source of error from the transfer. It is critical that all sources of error are reduced as much as is possible throughout the process.

As with any other GMP work, any unplanned events that occur during the transfer should be covered by a deviation. A full investigation should be performed so as the root cause may be identified. Communication between the two laboratories is key, particularly when determining if similar issues have been seen in the past. Remember that only if the root cause non-method related can the transfer experiment be re-run. The exact procedure for this will be based upon the quality system(s) of the laboratories involved in the transfer.

Report

As with the protocol, the report should be structured in a logical format with a copy of the transfer protocol appended for full traceability. Clearly it is not possible to add all data collected into the report, however, the content should be sufficient enough to allow the reader to have confidence that the analytical transfer has been successfully achieved and is therefore fit for routine use. As well as the report, if the method has been transferred from an external laboratory, other additional documentation needs to be created. This includes an in-house test method (with example chromatography) and specification. Finally, ensure that all documentation obtained from the transfer and sending laboratory has been archived.

Conclusion

Analytical method transfers are always required during pharmaceutical product development and are often not given the level of attention required. The strategy used in the execution is pivotal and takes into account a number of aspects, including the type of method, stage in the product life-cycle, stage of validation and experience of the receiving laboratory. This paper has outlined and discussed the key factors that should be evaluated to ensure that communication is free-flowing, and that any potential issues are identified early on in the process and adequately resolved ahead of the transfer activities.

RSSL have a broad experience in the successful transfer of a variety of analytical methods spanning a range of pharmaceutical product types, and our expert knowledge can facilitate an efficient and seamless transfer. To find out more please contact us on: +44 (0)118 918 4076, email enquiries@rssl.com, or visit www.rssl.com

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Steve has sixteen years' industry experience, having graduated in 2000 from Kingston University with a Bachelor's Degree in Pharmaceutical Science. He has spent his entire career to date working in the pharmaceutical sector and has gained all of his experience within a CRO environment, gaining exposure to a wide range of analytical techniques and product matrices. Steve's main area of expertise is Early Phase Development, Validation and Stability Testing of New Chemical Entities and Formulations mainly in Pre-clinical Development or Phases I and II.

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