Reference Laboratories Can Make Validation More Efficient

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Abstract

The validation of in vitro methods is a lengthy process encompassing multiple phases. It progresses from initial test development, through test optimization and prevalidation, to a formal validation assessment, and eventually to regulatory acceptance. Each of these phases relies heavily on the outcome of laboratory activities - even the regulatory acceptance step involves careful inspection of the data to determine their applicability to the regulatory need under consideration. The competence and experience of laboratories participating in each phase have a significant effect on the efficiency of the entire process. History has shown that the process is never as fast as we would like; however, it can be even slower if technical errors are made along the way. High-quality laboratory work is required to maximize the opportunity for success at each stage. This emphasizes the need for a group of experienced, competent laboratories (reference laboratories) capable of readily participating in any of the phases. Such laboratories should be able to conduct assays under GLP-compliant conditions, and should optimally be independent from the developers. Reference laboratories experienced in each of the phases are particularly valuable to the process since they will be able to help test developers at an early stage to design robust protocols that can withstand the rigors of validation and subsequent routine usage. They will also be able to support the successful implementation of assays to naive laboratories post-validation, and assist the regulatory agencies in training reviewers to correctly interpret data from newly approved in vitro assays.

Desired Attributes of a Reference Laboratory

- Independence from assay developers and manufacturers
- GLP-compliant
- Experience in the following:
  - Routine use of *in vitro* assays
  - Scientific and regulatory needs of industry
  - Requirements of regulatory agencies
  - Working under validation study conditions

Fundamental Research

Generally conducted in academic, government, industry or start-up companies. These laboratories often have limited experience with the requirements of a test system in a regulated environment.

Input of Reference Laboratory

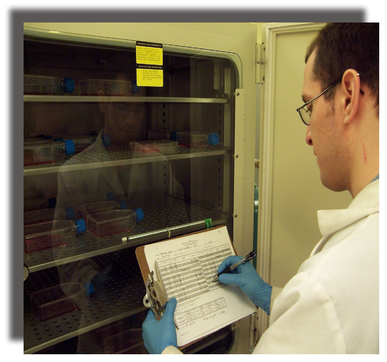
Provide information to the developers regarding:
- Limitations that the cost of the system could create
- Required robustness of system for large scale use
- Realities of scaling up to a GMP-like environment

Test Development

Investigations designed to find the optimal assay design and protocol that can be utilized reliably and reproducibly internationally. Initial studies to understand the predictive capacity.

Input of Reference Laboratory

Provide laboratory skills necessary to refine the assay methodology so that it is transferable and reliable. Apply experience from validation programs to develop detailed protocols and SOPs sufficient to be understood and correctly applied by naive laboratories.



Prevalidation

Using formalized studies to determine the transferability of the assay and its reproducibility both within and between laboratories. Continued studies to develop the database, define the prediction model and understand the predictive capacity.

Input of Reference Laboratory

Take leadership role of any segment of prevalidation and quickly oversee transfer of an assay to a secondary lab, implement reproducibility studies, and design initial performance studies to develop the prediction model.

Validation

Larger scale studies designed to test the proposed prediction model on a larger group of chemicals with known activity. Also assess reproducibility. These studies can be done separately or as a single unit.

Input of Reference Laboratory

Be available to serve as a testing laboratory with little delay. Conduct GLP-compliant studies in a timely manner, not constrained or preempted by other competing laboratory work. Can quickly train other participating laboratories in GLP-compliance, if necessary.

Regulatory Acceptance

Different regulatory agencies may require different processes and standards for accepting a new assay. For many national organizations, regulatory acceptance can occur with or without the conduct of a formal validation study. Whatever the specific process for an individual assay, regulatory acceptance will require that agency personnel become knowledgeable in the assay and develop confidence that it can provide the needed information.

Input of Reference Laboratory

Provide laboratory demonstrations of methods to regulatory management and reviewers, thus facilitating understanding and potential acceptance of the relevance of the assay endpoint.

National Agency Acceptance

Input of Reference Laboratory

Participate on expert review panels so that experienced user input can be available to guide the development of the technical aspects of Test Guidelines.

OECD Test Guideline

Input of Reference Laboratory

Provide laboratory-based training courses to industry toxicologists so that methods can be quickly adopted into routine use.

Routine Use By Industry

Conclusions

An increasing number of alternative methods need to be assessed to meet the growing legislative and scientific demands. In order to evaluate these methods in a timely manner, the validation and acceptance process must be as efficient as possible. Often progression through the validation process is unnecessarily delayed by method developers lacking information on regulatory requirements and exact industry needs, and subsequently by time spent in identifying testing laboratories that have the ability to execute validation programs without significant additional preparation and training. Importantly, final industry adoption of approved methods can be slowed by lack of experience and training.

One way to increase efficiency is to utilize a set of well qualified, experienced reference laboratories to assist numerous stakeholders, including method developers, industry scientists, validation authorities and regulatory agencies. These laboratories should be GLP-compliant and have trained staff that perform a variety of *in vitro* tests on a regular basis. This expertise could be quickly applied to any stage of the validation and acceptance process, and would significantly decrease the time elapsed between the first test prototype and routine industry use of a regulatory accepted method. The benefits of such a set of reference laboratories are clear – a way to provide financial support and thus ensure the existence of such laboratories should now be investigated.

One Way Forward

Finding an organization that meets <u>all</u> the desired attributes of a reference laboratory is very difficult. The technical staff must maintain a high quality level of training and proficiency in a wide variety of *in vitro* techniques. This generally occurs only in a laboratory that regularly conducts a wide range of *in vitro* assays. One potential candidate is a GLP-compliant contract research organization (CRO) that offers a diverse set of alternative methods. A CRO has the added benefit of understanding the needs of industry and the potential industrial uses for a new method.

However, one substantial obstacle for a CRO in considering the Reference Laboratory concept is the balance between the demands of commercial work and that of validation projects. Validation contracts rarely cover the full costs of the project and industry's commercial needs can often take priority. To overcome this obstacle some type of supplemental funding and a strong corporate commitment to alternatives is necessary.