

## The importance of supplier qualification for vendors of materials used in *in vitro* assays

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### Abstract

Pre-clinical assays, including *in vitro* assays, rely heavily on suppliers who provide essential products or services. In the current regulatory environment, the burden is placed on the users of these products or services to ensure that the methods employed at the suppliers' facilities meet a sufficient level of quality. Variable results for the same assay controls over time could indicate high lot-to-lot variability of the test system or of critical assay components. Though monitoring assay controls is useful to help evaluate supplier quality retrospectively, instituting a supplier qualification program provides a proactive way to document that suppliers of test systems and critical components consistently adhere to the high standards necessary to support work performed in compliance with Good Laboratory Practice (GLP) guidelines. A strong supplier qualification program, consisting of pre-qualification audits and regular evaluations, provides a framework for auditing both small and large scale suppliers against the appropriate standards for each laboratory's *in vitro* testing program. We present here a supplier qualification program we have developed that has helped our suppliers make significant improvements in the quality of materials we use to perform our GLP dermal and ocular irritation studies.

**Keywords:** supplier qualification, quality assurance, Good Laboratory Practice, audits, test system

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### Introduction

The Organization for Economic Cooperation and Development (OECD) defines a test system as "any biological, chemical or physical system or a combination thereof used in a study" (OECD, 1998). Test systems for *in vitro* assays can vary widely (consequently involving a wide range of suppliers) and include commercial cell suppliers and repositories, commercial tissue engineering and tissue model developers and suppliers, and abattoirs (Table 1). Variations in the quality of the test system or of critical assay reagents (critical components) can negatively impact the performance of the *in vitro* assay. If an assay is performing poorly, it can be difficult to distinguish between test article induced changes in the test system and changes caused by a poor quality test system or critical components. Once a strong in-house quality assurance program has been established (Ulrey, 2005), a program should be developed to monitor the quality assurance or quality control programs in place at the facilities supplying the test systems and critical components.

Although some follow US Food and Drug Administration Good Manufacturing Practices

(GMPs) (21 CFR 820) or are certified as meeting International Standards for Quality Management Systems (ISO 9000), many suppliers for *in vitro* test systems or critical components do not meet these criteria. A thorough supplier qualification program can increase the confidence of testing facilities and their clients in the results generated by an assay using prequalified test systems and critical components. We present here some guidelines for developing a supplier qualification program, along with some specific examples from the supplier qualification program we have initiated at IIVS.

### Discussion

#### Points to consider while developing a supplier qualification program

Although the core components of the audit remain the same across all test system manufacturers, different suppliers should be held to different standards based on their product. (See Table 1 for examples of *in vitro* test systems. For example, a cell bank or tissue manufacturer would be held to a higher standard of quality than an abattoir. The supplier qualification program at IIVS was developed with

Table 1: Examples of *in vitro* test systems

<b><i>In vitro</i> test</b>	<b>Test system</b>	<b>Suppliers</b>
Bovine Corneal Opacity and Permeability Assay	Bovine corneas	Abattoirs (providing normally discarded material)
3-Dimensional Tissue Construct Assay	EpiOcular™, EpiDerm™, EpiSkin™, etc.	MatTek, SkinEthic, L'Oreal
Corrosivity	CORROSITEX™ Chemical Detection System	In Vitro International
Cytosensor Microphysiometer™	L929 Cells	American Type Culture Collection
Neutral Red Uptake Assay Phototoxicity Assay	BALBc/ 3T3 cells	American Type Culture Collection

Table 2: Requirements for Quality Assurance of Test Systems in GLP Studies.

<b>Regulations</b>	<b>Requirements for Test Systems</b>
<b>Organization for Economic Cooperation and Development Series on Principles of Good Laboratory Practice and Compliance Monitoring (ENV/MC/CHEM(98)17)</b>	Number 14 -Application of GLPs to In Vitro Studies <i>"test facility management should ensure that the test facility supplies meet requirements appropriate to their use in a study. Certain in vitro studies may necessitate the use of proprietary materials or test kits. Although the OECD consensus Document on Compliance of Laboratory Suppliers with GLP Principles states that material to be used in a GLP compliant study should be produced and tested for suitability using an adequate quality system, thus placing the primary responsibility for their suitability on the manufacturer or supplier, it is the responsibility of the test facility management to confirm that these conditions are adequately fulfilled through assessment of the suppliers practices, procedures and policies."</i>  5.1.2. the integrity of the physical/chemical test systems should be ensured  8.2.5.a. [Protocols must include] Justification for selection of the test system  8.2.5.b. Characterization of the test system, such as the species, strain, substrain, source of supply, number, body weight range, sex, age and other pertinent information
<b>U.S. Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) Part 58 – Good Laboratory Practices</b>	Study Directors are responsible for assuring that test systems are as specified in the protocol which often list specific information about test system characteristics as justification for use of the test system in the assay.
<b>U.S. Environmental Protection Agency (EPA) Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) to CFR Part 160 – Good Laboratory Practices</b>	Study Directors are responsible for assuring that test systems are as specified in the protocol which often list specific information about test system characteristics as justification for use of the test system in the assay.  160.120.a.5. [Protocols must include] Justification for selection of the test system
<b>U.S. EPA Toxic Substances Control Act (TSCA_ 40 CFR Part 792 - Good Laboratory Practices</b>	792.33.d. Test systems are as specified in the protocol.  792.120.a.5. Justification for use of the test system.
<b>The Good Laboratory Practice Regulations 1999 (UK)</b>	Part V. 1. (2) The integrity of the physical/chemical test system should be ensured

tissue manufacturers in mind, but the basic concepts described here can be applied to multiple types of suppliers.

It is mutually beneficial to maintain an open and candid dialog about quality control practices. Open communication provides an opportunity for suppliers to understand how their products are being used, and allows them to advise the testing facility of proper handling techniques for their material. Suppliers also learn how their materials perform off site, which may allow them to improve their products.

When performing any facility audit, keep in mind that some suppliers might be reluctant to allow testing facility auditors to view records which might expose a proprietary manufacturing process. A "sanitized" copy can be provided to the auditor for use in evaluating compliance with documented facility

practices. Information on equipment maintenance, training, adherence to SOPs, proper oversight of the manufacturing process and handling of Out of Specification results can still be obtained from partial or sanitized records.

Each supplier qualification audit should culminate in the generation of a report providing formal documentation of practices at the facility at the time of the visit. It can also include suggestions for improvements. This documentation will provide the testing facility historical information on the practices at the supplier's facility and how they have been modified over time. Suppliers should be encouraged to respond to the report and any action items remaining open should be re-assessed during a later audit.

## Rationale for instituting a supplier qualification program

### GLP Compliant Laboratories

Testing facilities conducting *in vitro* assays in compliance with GLP guidelines are directly responsible for ensuring that the test systems and critical assay components used in each study are of a suitable quality to assure that the data received are reliable and reproducible (Table 2). Government inspections are not conducted at supplier facilities unless they are registered under Good Manufacturing Practices (GMP) in the United States or their International equivalent, the *in vitro* testing community itself is currently the only body capable of holding non-GMP or non-ISO suppliers to a defined state of quality. The majority of suppliers (particularly test system suppliers) do not participate in any audit programs; therefore, both prospective and yearly monitoring audits by testing facilities are necessary to assure that the GLP requirements for supplies used in studies are being met.

### Non-GLP Laboratories

Contract Research Organizations (CROs) and test article providers (Sponsors) are responsible for making decisions based on the data obtained from assays performed using test systems and critical supplies. CROs and sponsors expect test systems and supplies to be consistent within each manufacturing lot and between lots over time. Inconsistent assay performance could result from poorly defined production methods, inadequate training, or improper release criteria at the facilities that manufacture test systems or critical components.

Suppliers of *in vitro* test models invest a great deal of time and resources in developing these novel systems. Having defined processes in place for each step of production, as well as for training and documentation, also benefits the supplier by ensuring they maintain scientific expertise related to their products even if personnel leave. It would also be in the supplier's best business interest to assess the controls in place to maintain quality in the scale-up process from prototype design to manufactured product. There is a large difference between an academic production setting and a manufacturing production setting. Adequate quality controls are vital to have in place when moving to a larger manufacturing scale to assure that the product remains consistent during the process.

An assay which must be repeated due to sub-standard test system or supplies ultimately costs both testing facilities and suppliers time and money. An opportunity exists to control a potential source of variability by requiring suppliers to implement a thorough quality control program. At IIVS, we saw a marked decrease in variation for positive controls

in one of our *in vitro* test systems after initiating an annual vendor audit program (Fig. 1), illustrating the positive impact a supplier qualification process can have on consistency in performance of a test system over time.

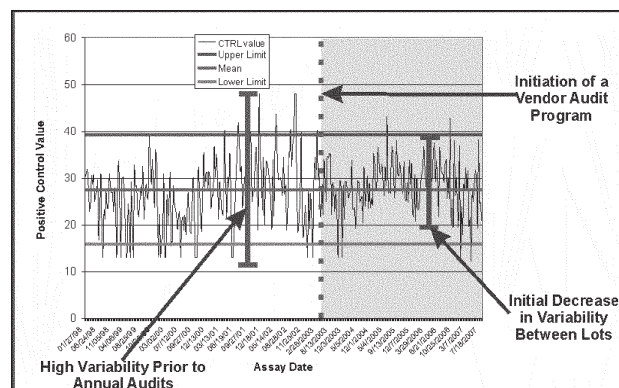


Fig. 1: Impacts of a vendor audit program on the results of the in-house positive control.

Historical positive control data demonstrates reduced average variation of the test system after a vendor audit program was initiated. The acceptable range for a usable assay falls between the upper and lower limits.

### General supplier audit points

Listed below are points we recommend including in audits of manufacturers who supply *in vitro* test systems and critical components. These points cover the production processes, training, and documentation and form the core components of a formal audit (See Fig. 2 for an illustration of this process).

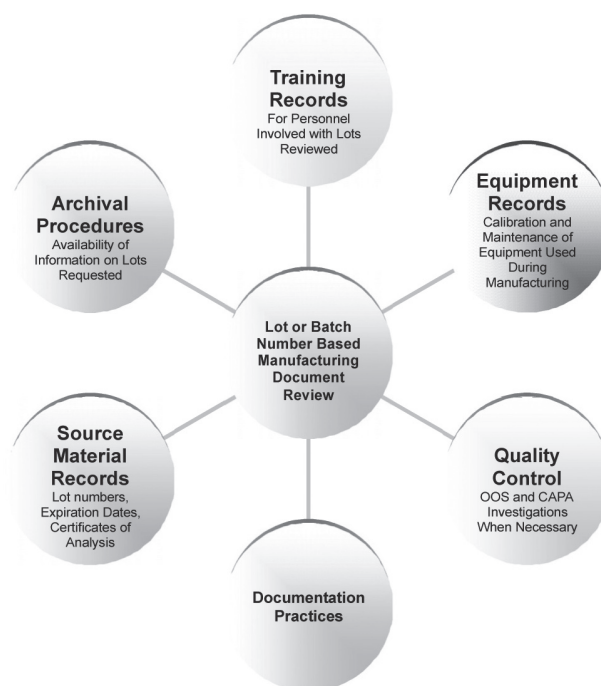


Fig. 2. Components of an audit.

Starting with the lot or batch of test system used (center), all additional areas can be evaluated through examination of applicable documentation.

*Defined and Management approved processes should be in place across the organization. The following areas should be included:*

- Quantities of components, critical times, and appropriate ranges should be defined for each process.
- Effects of deviations from defined processes should be identified through a formal Corrective and Preventative Action (CAPA) Plan or from basic research involved in creating the product.
- A document control system should promote and maintain stability within the manufacturing operations.

*Training – Employees should be trained in the following areas:*

- The production process and equipment utilization.
- Proper documentation practices.
- Employees should receive on-going training to ensure adherence to current procedures. This is particularly important for long-term process control.

*Equipment maintenance programs for a facility should include:*

- Established control over equipment (incubators, refrigerators, etc.) parameters.
- Temperature logs documenting proper functioning of all equipment used in the manufacturing process.
- Maintenance logs for recording routine, scheduled maintenance (calibration and cleaning) and non-routine maintenance, whether it was performed by facility personnel or contract equipment service providers.
- Out-Of-Specification (OOS) investigations performed when equipment functions outside of its acceptable parameters. The impact of equipment malfunctions to product quality should be discussed in the documentation.
- A use log tracking the lots of product that have come into contact with certain pieces of equipment, depending on the manufacturing environment.
- Cleaning procedures used on special equipment may need to be tested to assure that they are sufficient to adequately clean the equipment without leaving any potentially harmful residues.

*Documentation across the organization should be standardized as follows:*

- All defined processes should be documented in approved Standard Operating Procedures SOPs (or equivalent) and readily available during the manufacturing process.
- Batch records should be created during the manufacturing or isolation of the product that

provide evidence that the approved processes were followed. These records include:

- o The person responsible for each step in the process
  - o Verification that appropriate amounts of reagents were used and that processes were carried out for the specified amount of time
  - o Equipment used and relevant performance parameters
  - o All primary documentation should follow good documentation practices as defined in the various regulations (and summarized below).
- Changes made to the documentation should be explained. The original entry should not be obscured and the person who made the change should be clearly identified.
  - Deviations from the SOP should be documented and include an assessment of potential product impact.
  - A documentation review should be performed by production staff (especially primary manufacturing records) and by someone not involved in the production and without any vested interest in the release of the lot performed prior to shipment (if applicable).
  - Training and equipment maintenance documentation should be maintained and be easily accessible.
  - Secure and accessible archives should hold all completed facility documentation.

#### **Additional audit points relevant to tissue models used as test systems.**

In addition to the core audit components above, additional points arise when auditing tissue construct manufacturers, particularly those utilizing human cells. Extra care is needed to confirm that the manufacturer can legally use these cells for profit, and special efforts are needed to minimize contamination throughout the entire manufacturing and shipping process.

*Points concerning product ownership:*

- Documentation showing that a legal source of cells was utilized during the tissue production process should be retained.
- If human cells were used, identity of the donor should be confidential.
- Manufacturers should be in compliance with applicable laws governing the use of human tissue for profit.

*A formal lot release testing program should consider the following:*

- Procedures (validated by the manufacturing company) should be in place for lot acceptance testing, and the test system should

meet standardized defined specifications before release.

- Out of Specification (OOS) results should be investigated, as should any drift or variation over time.
- Review of batch records maintained during production could be included in pre-release quality control.
- Lot release testing could culminate in the creation of a Certificate of Analysis for the each lot that can be shipped to testing facilities along with or ahead of the tissue.

Quality control measures may be necessary for critical components. Points to consider are:

- Pre-qualification of critical components prior to use may be necessary (Fig. 3).
- An initial quarantine may be required for material that has not yet been qualified.
- Batch records should be maintained for all material created or supplemented in-house.
- Test for sterility as needed.
- Certificates of Analysis should be supplied by vendors for any purchased components.
- Good documentation should allow each component to be traced back to its source.
- Store released, rejected and quarantined critical components separately.

Shipping Validation – A shipping validation may need to be performed by the manufacturer working with the help of a second party. A shipping validation study consists of:

- Verification that the tissue functions properly after shipping by testing controls at the manufacturing site prior to shipping and then again at the testing site after shipping (Fig. 4).

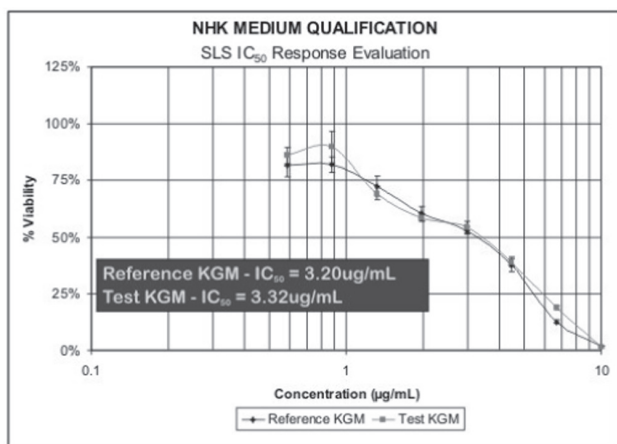


Fig. 3: Side-by-side testing of both reference and a new lot of KGM media prior to use in cell culture. Media qualification results of a trial run on 19-May-2004. Reference lots: KBM = 01102905, SingleQuotes® 08100950. Test lots: KBM = 0110532, SingleQuotes® = 08101273. In this example, the new lot was found to be acceptable.

- Checking temperature control mechanisms while the tissue is in transport.
- Verification of proper tissue characteristics upon receipt after shipment overseas, which may expose the tissue to radiation.
- Assurance of compliance with national or international safety and shipping regulations.

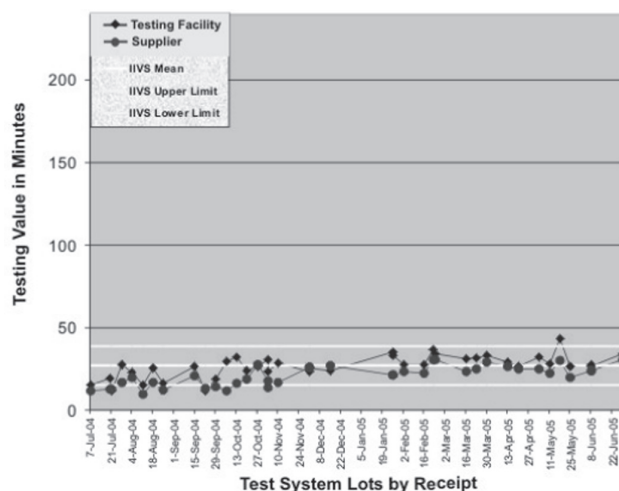


Fig. 4: Shipping validation study.

Performance of a test system under identical exposure conditions pre and post shipment. NOTE: This graph is constructed to reflect the 240 minute dynamic testing range of the assay.

## Summary

Implementing a good supplier qualification program increases the confidence of testing facilities and their clients in results generated from assays using test systems and critical components purchased from outside suppliers. Such a program should include (at a minimum) initial and yearly audits of the defined processes, documentation, equipment maintenance and staff training at the manufacturer's facilities. We have implemented a supplier qualification program at IIVS and have noticed an improvement in the performance of our test systems as demonstrated by monitoring our historical control data.

GLP compliant testing facilities are ultimately responsible for ensuring the quality of their test systems and critical components regardless of whether they are generated in-house or purchased from outside suppliers. Since there is no formal process for qualifying suppliers of *in vitro* test systems at the regulatory level, the *in vitro* testing community itself is the primary force setting quality standards for suppliers. The more involved we become in monitoring our suppliers and vendors, the higher those standards will become. This will allow the *in vitro* testing field to grow stronger and more readily accepted by regulatory agencies.

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