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METHODS & REVIEWS

Analytical Laboratory Quality: Part I. General Quality Practices

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Once a biotechnology product reaches the final stages of development, the types of quality practices required in the laboratories performing the analytical testing are clearly defined in the applicable regulations. Long before this stage, though, there are innumerable tests and studies conducted in biomolecular facilities that provide critical information upon which product development decisions are made. While sound scientific practices will guide the management of the best of these laboratories, there are several additional operational elements that can significantly enhance the utility of the data to commercial clients. Such laboratory quality practices can also provide considerable benefit to the facility itself, engendering higher confidence in the day-to-day operations within the laboratory. Most of these practices can be simply implemented with pens, notebooks, and diligence. (J Biomol Tech 2001;12:4–10)

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The biotechnology revolution established our ability to produce, reproducibly and in large quantities, desired products of biologically based processes such as rDNA proteins, antibodies, peptides, oligosaccharides, and nucleic acids. Along with this capability came the need for testing such products to determine their nature, assess their suitability for use, and provide ongoing analysis of their routine production. Between the "Aha!" moment of discovery and the regulated manufacturing and testing of the final product lies many additional laboratory analyses. Some of the same bioanalytical methods initially used in research and development (R&D) laboratories for the discovery of many of these biomolecules are routinely being used to test the quality and consistency of manufactured biologic products. For these analyses, there are several attributes of the methods to be considered beyond those found valuable in discovery. Similarly, there are additional aspects to be considered of the testing laboratories in which these methods are conducted, especially if the data may ultimately be used in support of product licensure. If you are an R&D facility conducting analytical testing of biomolecules or a client seeking such testing from a laboratory, you should be aware of laboratory quality practices and of applicable compliance requirements.

QUALITY ELEMENTS OF A LABORATORY: HOW DOES IT RATE?

Table 1 provides a brief quiz on selected laboratory operations. Determine which answers best fit the activities of your facility or the facility with which you are working. If a, b, h, i, and l were answered, it is probably a high-quality R&D facility. If any of these plus e, g, j, and o were answered, it is a high "Quality" facility, meaning that elements of quality assurance and control are being incorporated into routine activities. If c, f, k, m, n, and p were answered, it is

TABLE 1

Quiz for Assessing Laboratory Quality Practices

Fill in the blank with as many items (letters) as apply:

"The analytical laboratory routinely_____"

a. Documents the identity and testing scheduled for incoming samples.
b. Records sample preparation and testing steps in notebooks or workbooks.
c. Can produce documentation that tracks laboratory activities from receipt of a testing sample to the dispensation of data for client samples designated "GLP testing."
d. Checks the operation of the laboratory freezers by touching the cold surfaces with bare fingers.
e. Records the daily temperature of all thermally controlled equipment in a log book.
f. Continuously records the temperature of controlled equipment with chart recorders, signs and dates each new chart, and archives the used ones.
g. Refers to vendor-supplied instruction manuals for operation of major instrumentation.
h. Uses experienced professional judgment when operating major instruments.
i. Has first-rate scientists and technicians working in the laboratory.
j. Has the curriculum vita of each scientist and technician in the laboratory on file.
k. Has documented method training protocols that each scientist or technician must complete before routinely performing those analytical methods in the laboratory.
l. Determines that instruments are operational when acceptable sample data are obtained.
m. Runs established system suitability standards to verify the validity of each analysis.
n. Has instrumentation on routine calibration and preventative maintenance schedules.
o. Records instrument operations, troubleshooting, and repairs in an instrument logbook.
p. Follows validated method protocols, recording and justifying any deviations from the established procedures.

well on its way to withstanding a U.S. Food and Drug Administration (FDA) audit! If d was answered, a calibrated thermometer is strongly recommended.

Many of these measures are already performed by careful scientists whether the goal is to attain a compliance-based level of quality control or not. For these individuals, the integrity of the laboratory is enhanced by providing sound management of facility activities. However, to become a Quality laboratory, additional measures may be needed (Table 2). What measures are needed and how they affect the nature of the analytical testing being performed falls within the realm of regulatory compliance requirements for specific test samples.

Apart from demonstrating good management, there are many benefits to establishing basic laboratory quality practices. Repeating tests because an instrument was not in good repair, the wrong sample was used, or an inappropriate method was applied wastes money and time. Worse, losing rare samples or unique data or releasing inaccurate results can be disastrous. In time, the laboratory's reputation will suffer. When a research study yields a "hit" molecule, the supporting analytical data should not have to be repeated just to get traceable, documented results. This becomes most critical when such small amounts of sample material are initially generated that repeat analyses are not even possible.

Even simple laboratory quality control measures can yield multiple benefits for the facility and the client. Waste is minimized by using designated materials for specified tests. Samples are handled more reliably when a tracking system is followed. Results are not jeopardized by having used expired reagents. Good documentation practices save time when troubleshooting problems and tracking performance trends with laboratory instruments and methods. Defined training plans expedite the productivity of new hires. Each of these practices result in more efficient activities, which can provide incremental (but significant) cost savings. Moreover, clients who are confident about the quality control of a facility's operations can further its reputation for excellence.

DIFFERENCES AMONG DISCOVERY, DEVELOPMENT, AND DISPOSITION TESTING

Analytical testing facilities can provide services ranging from supporting early product discovery to performing lot release testing (ie, determining the pass or fail disposition of products manufactured for sale). Reasons for implementing specific quality practices are typically based on the stage of development of the sample. There are significant differences in the compliance regulations placed on the laboratory depending on

TABLE 2

General Quality Practices of Analytical Laboratories

1. Reagents and Materials
A. *Good:* All chemicals, reagents, and critical materials (eg, PVDF membranes, HPLC columns) are handled and stored according to the manufacturer's instructions and used within the vendor's expiration dates. *Better:* In addition, an inventory log of laboratory materials is maintained, with expired chemicals always being purged from stock.
B. *Good:* The preparation of each hand-made reagent solution is recorded, along with the name, vendor, lot number, and expiration date of each component. *Better:* In addition, these reagents are assigned in-house expiration dates. For example, an aqueous buffer solution may be labeled to expire 2 months after preparation.
C. *Good:* The type and source of water used for each solution is recorded. (Bottled water may be recorded as a reagent, with lot numbers and expiration dates.) *Better:* In addition, water purification system checks (eg, conductivity) are performed daily, maintenance (eg, changing of cartridges) is performed monthly, and all system activities are recorded in a laboratory log book.
2. Samples and Standards
A. *Good:* Samples are logged in on arrival, including description, date, and storage status (eg, room temperature, 4°C, −70°C). *Better:* In addition, a unique identification is issued for every sample using a system that prevents accidentally assigning the same information to different samples.
B. *Good:* Samples are stored at their required temperatures and conditions (eg, with desiccant). *Better:* In addition, these substances are held in labeled locations, they are segregated from other materials in that same location, and the temperature of the holding location is continuously monitored.
C. *Good:* Sample preparation details are recorded. *Better:* Sample preparation, including the lot numbers and expiration dates of any solutions or critical materials used, are recorded into a bound notebook or controlled workbooks, signed, and dated.
D. *Good:* Known materials are periodically tested to confirm the performance of each analytical method. *Better:* Qualified, traceable standards are used in conjunction with test samples to confirm the performance of each method. When characterized samples of the test article are available, they are used as an additional "standard" to assess method performance.
3. Equipment
A. *Good:* Small equipment is checked periodically for adequate performance (eg, rotators, pipettors, spectrophotometers, shakers, pH meters). *Better:* Routine checks and maintenance are performed. For example, pipettors are tested to deliver expected volumes. Before using pH meters, the condition of the electrode is noted, and a two-point calibration using fresh standard pH solutions is performed. Spectrophotometers are calibrated regularly. These activities are logged and signed.
B. *Good:* Controlled temperature equipment (eg, water baths, cold boxes, freezers, incubators) are regularly and frequently monitored. For example, a single temperature log can contain manually recorded readings each morning for the equipment used by the laboratory. The temperature of items used for short incubations can be recorded in the experimental notebook for the start and end of incubation times. *Better:* Continuously recording temperature charts are installed on equipment holding samples around the clock. Charts are replaced regularly; used charts are signed, dated, and archived.

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TABLE 2

General Quality Practices of Analytical Laboratories (continued)

3. Equipment (continued)

C.
Good: Complex instrument systems (eg, HPLCs, DNA sequencers, mass spectrometers) are routinely checked and tested, with performance results noted in the instrument's log. For example, operation and troubleshooting of an HPLC system are documented in a log book for that instrument.
Better: In addition, these undergo scheduled preventative maintenance by qualified service personnel. Maintenance and service records with copies of chromatograms (or other data) demonstrating suitable performance after repairs are also included in the log and dated.

4. Methodology

A.
Good: All sample preparation and testing activities are documented when performing an analysis.
Better: Standard operating procedures for routine analyses are written by the laboratory and followed, particularly in facilities with multiple or novice operators.
B.
Good: Sound experimental design and appropriate system suitability criteria are used for each investigation. For example, blanks (eg, solvent only) and known standards are run before each analysis of a sample so that method, instrument, and operator performance are confirmed before sample analysis.
Better: In addition, routine methods are qualified or validated for their intended use.

5. Data

A.
Good: All raw data are uniquely linked to each analysis.
Better: Raw data are identified and recorded in a laboratory notebook, signed, and dated.
B.
Good:: Details of the analysis are recorded with each test. For example, the integration parameters used when analyzing sets of chromatograms are recorded.
Better: Methods of data analysis are confirmed or validated using known standards appropriate for each technology. Types and versions of analytical software used are noted for each test.
C.
Good: The analyst double-checks her or his data and reports to confirm integrity.
Better: An independent, qualified authority also reviews the data and reports to verify the analyst's conclusions, and then approves the information for release.
D.
Good: Additional copies of laboratory data can be obtained from each analyst when needed.
Better: A coordinated archiving system is used for retention and retrieval of analytical data generated by the laboratory. If an electronic system (i.e., PC, server) is used to generate or store data, measures are in place to assure the integrity and security of the information.

6. Personnel

Good: Scientists and technicians are competent and have documentation in their employee files for their experiences (eg, curriculum vitae).
Better: A training plan is established for each technique. Operators demonstrate their proficiency (eg, by running known standards) before performing routine sample analysis with that technique.

how the data are to be used.[1] For cutting-edge scientific discovery or for early-stage product development, the kinds of "small q" quality measures previously described may be sufficient. Methods may be developed and modified as needed to obtain the data used to make early decisions about molecular identity and product feasibility. In these cases, good experimental controls may be adequate to confirm testing reliability. For later, developmental phase characterizations, analytical laboratories should aim toward "capital Q" quality measures. Traceability of materials, confirmation of test sample status at all times while in the laboratory, documentation of activities, and archiving of data strongly support the integrity of analyses that may be used in product assessment decisions. At this stage, products may begin to fall under preclinical quality regulations.

For products entering scale-up, manufacturing, and disposition testing, specific governmental regulations may apply. In the United States, there are two major FDA regulatory documents published in the Code of Federal Regulations (CFR) that regulate biotechnology product development and manufacturing. These are current Good Manufacturing Practices, simply referred to as the cGMPs,[2,3] and the Good Laboratory Practices, or GLPs.[4] Other countries have similar types of regulations.[5] These documents are available from numerous regulatory web pages (eg, use a search engine and query "regulatory affairs"). FDA documents can be obtained directly (http://www.fda.gov). Additional regulatory information can be found in guidance documents from professional quality agencies such as the American National Standard Institute and the American Society for Quality Control (ANSI/ASQC).[6]

Although many laboratories practice what in casual terms could be called "good laboratory practices,"[7] the official GLPs are a specific set of FDA requirements for preclinical laboratory studies conducted to support product development in the animal toxicologic phase. The GLPs apply to the procedures used to characterize the test article (ie, substance under study, typically a test solution) and to determine its stability, homogeneity, and concentration. Included in the GLP regulations are requirements that are applied to contract facilities performing selected parts of the total study. Portions of these may be applied to analytical laboratory operations, depending on the role the laboratory has in the design, performance, documentation, archiving, and quality review auditing of the analyses.

In some cases, analytical resource facilities may perform actual final release (ie, disposition) testing on products for sale.[8] Analytical tests such as protein sequencing, amino acid analysis, or mass spectrometry may be among these procedures. In the United States, cGMP regulations must be followed for the testing of these materials; other countries have similar regulations. In the cGMPs, there are significant regulatory requirements for virtually every aspect of laboratory operations, including the physical environment in which the laboratory is housed and the movement and storage of materials within the facility.[9] An analytical laboratory that is designated cGMP must meet numerous stringent quality measures as described in the regulations.[10] As with the GLP regulations, the burden is on the laboratory to understand and implement them.

In establishing GLP or cGMP laboratory conditions, a facility does not become "certified" for these designations. Although the quality principles that apply to each set of practices are outlined in the appropriate regulations, the facility itself must interpret how its operations will be managed to meet their requirements. When the facility is audited by the regulating agency, observations of noncompliance (called 483s for the FDA form number on which they are written) are issued if the CFR requirements are not deemed to be adequately implemented.

One notable case involving Barr Laboratories[11] illustrated the differences between the measures that are broadly outlined in the regulations versus FDA audit findings on how a laboratory did (or did not) implement them. The Barr case represented a watershed event in defining laboratory quality control principles such as validation, methodologies, evaluation of test results, and application of statistical analyses.[12,13] As a result of the Barr decision, many initiatives were undertaken to update and clarify regulatory guidelines.[14]

To assess the level of quality in an analytical facility, an audit should be performed, even if it is informal. Table 2 includes a listing of recommended issues for both q and Q levels of quality. "Good" measures are aimed at laboratories desiring a q level of quality. "Better" measures enhance the Q in Quality practices. Not included are specific items for GLP and cGMP compliance; facilities desiring to meet these regulations should obtain the complete federal regulations and review them in detail. Several publications available for guiding audits of regulated laboratories can be valuable resources for users and managers of these facilities.[15–18] Most reference the applicable requirements across different regulatory bodies for each aspect of compliance. For convenience, some even include complete versions of the actual U.S. and international regulatory documents as well as guidance documents from professional quality organizations.

One additional mechanism for assessing the level of quality in a bioanalytical laboratory is through the routine performance trials that are sponsored by the Association of Biomolecular Resource Facilities (ABRF,

Rockville, MD, www.abrf.org). For more than 10 years, the ABRF has been conducting voluntary international performance trials for methods such as protein sequencing, amino acid analysis, and DNA sequencing.[19] Laboratories that choose to participate in these trials are sent blinded samples for analysis, and they return their data for anonymous compilation with data from other facilities. The results indicate the actual level of field performance for the given analytical method. Typically, the results are reported by instrument type, age, and any significant details of the methodology employed. These data are particularly useful in evaluating the ruggedness of new methodologies as well as the stamina of aging instrumentation. They can serve as the rolling benchmark against which a laboratory may measure its own performance. Such a mechanism is endorsed by the ANSI/ASQC Standard Q2: "Where such programs exist, each laboratory should participate periodically in an established interlaboratory test program designed to evaluate the status of laboratory testing or analytical proficiency."[6]

FOR ALL LABORATORY ACTIVITIES: "IF IT ISN'T DOCUMENTED, IT DIDN'T HAPPEN"

Although this historical military phrase is often overused, it is not to be underestimated when conducting high-quality and high Quality activities. Documentation of operational and experimental details can provide the critical link between what was done versus what can be proved under audit. Equally important, these records can serve as a laboratory activity control chart, so that ongoing data interpretation and method troubleshooting can be based on reliable information. For example, if high-performance liquid chromatography (HPLC) chromatograms from several unrelated test samples begin to develop spurious peaks, a review of the reagent log books may reveal a common reagent solution that became contaminated. This would aid in troubleshooting the problem and could support justifications for not considering the contaminating peaks to be impurities in the test samples. If a laboratory routinely records the results of system suitability standards on a statistical control chart, the performance of the instrumentation systems can be observed independently of the performance of the test articles. Early detection of performance problems can allow an operator to investigate and intervene before a critical test is needed, saving time and the potential loss of important samples.

Good documentation practices should be established and enforced within the high-quality laboratory and are mandatory in the Quality laboratory.[7,20] All personnel should adopt the habit of signing and dating data entries, activity logs, and experimental procedures. Dark, indelible ink should be the writing medium of choice, and bound or paginated workbooks should be used. All final reports should be reviewed by an independent individual who is qualified to approve the results. Having this second-level check on the information before it is sent out can provide an additional measure of quality assurance for the laboratory and for their clients.

Unless all raw data are given to the client to retain, a safe and secure storage area should be designated for housing all archived reports, including electronic backups of computer programs and computer-generated data. When archiving computer-generated data, remember that a disk containing the data without an application with which to access it is like having no data at all. Print hard copies, or securely save application programs and maintain functional computers on which to run them. One major cGMP regulation, 21 CFR Part 11, applies to the electronic capture and storage of information used on regulated manufacturing and testing facilities.[21] For general quality practices, even if raw data are immutable, instances of review and reanalysis should be documented.

CONCLUSIONS

Although some of these general quality practices may seem daunting to implement, most only require pens, notebooks, and diligence. A laboratory may designate one daily record book for monitoring equipment such as refrigerators, freezers, and water systems; assign a log to each major analytical instrument; and have every analyst use a bound notebook. A system for the holding and tracking of samples and data can be established. Instructions for the performance of routine analyses can be written; analysts can test known samples and compare their data with expected results for training or method performance assessment. A system whereby final data are reviewed and approved by a designated laboratory authority before release to clients can be established.

The consistency with which these measures are applied will determine the real level of quality within the laboratory. A few minutes each day spent on implementing quality practices are far more beneficial and less costly than hours spent trying to decipher the results of bad laboratory habits.

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