by Paul Smith

Reprinted from *American Laboratory* March 2015, Volume 47, No. 3

Compliance in Regulated Laboratories

Before analytical results can be generated, a laboratory requires a suitable calibrated instrument, a trained analyst, an approved/validated method, appropriate reference materials, a standard operating procedure to help ensure the instrument is used in a consistent and reproducible manner and samples to test. When considered from a "compliance principles" perspective, these points are essential to support/defend the validity of the analytical results and can be thought of as almost independent of the industry in which the instrument is used. At a high level, the "compliance life cycle" a laboratory follows for introducing a new laboratory instrument—from initial business investment through justification, managing and approving the analytical results generated—should:

- Be based on sound business and scientific rationales
- Consider the materials to be tested
- Define how the instrument will be used
- Document results calculation and reporting
- Support the decisions the results will be used to make.

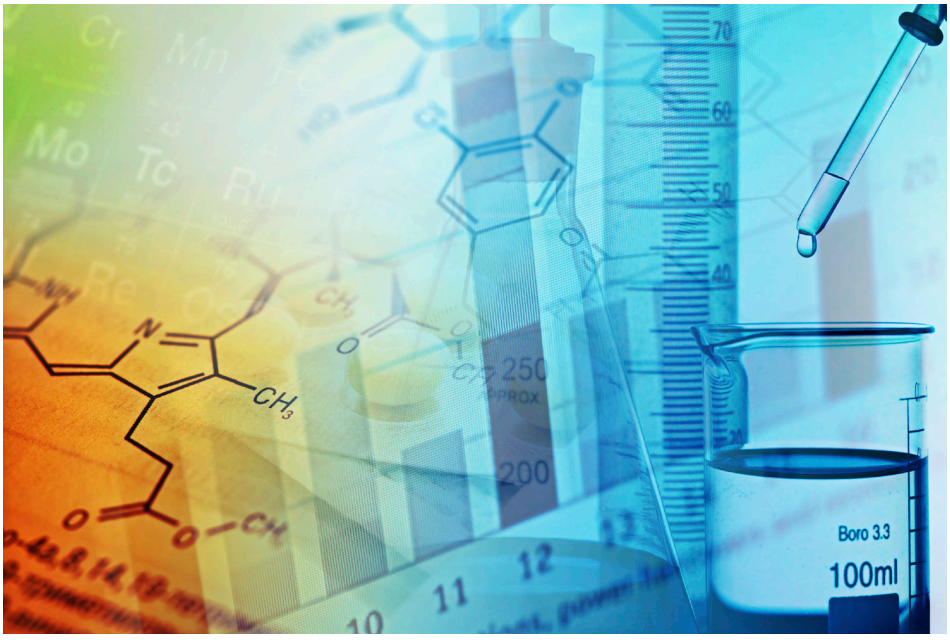
The various regulated industries approach the subject of laboratory compliance in different ways and can use compliance terms in unique ways. It's not even unusual for laboratories in different parts of the same organization to have individual approaches to compliance or to use different terms. These differences can limit the exchange of information and sharing of best practices. Often, the jargon used in a particular sector or industry can make it hard for outside laboratories to understand. Differences may only become apparent where organizations decide to harmonize compliance approaches or where an analytical method is transferred from one laboratory to another.[1] The term "calibration" can itself have a very specific meaning and definition (e.g., an ISO 17025-accredited calibration service), or it may have a more general meaning in the laboratory. A metrologist will work with a definition of "calibration" that differs from that of an analytical scientist, laboratory manager or auditor. When the expression "calibration" is used in a pharmaceutical testing laboratory, it may have a range of possible meanings, depending on the quality management system in place and the communication preferences of the person. The expressions "Calibration, Qualification, Validation and Verification" are examples of compliance terms that are sometimes used more as labels that represent a type of activity rather than the very tight definition used in an ISO standard. In the interest of clarity, it may be necessary to request both an explanation and an example, the latter providing context and thus enabling a more meaningful compliance discussion.

While the *Code of Federal Regulations* (*CFR*)[2] often provides general guidance on the systems and policies a laboratory needs to have in place for compliance, it does not necessarily define the exact details or processes a laboratory must follow to be compliant. For pharmaceutical laboratories, one way to interpret this position is that the *CFR* provides the Good Manufacturing Practice (GMP) and it is up to the organization to make it current (e.g., cGMP). Generally, a Quality Management System (QMS) will provide the underlying compliance framework that satisfies general regulatory requirements such as the *CFR*, as well as specific procedures and SOPs to satisfy the essential details of how laboratories remain compliant.

One potential risk in laboratories is that personnel may be well trained in the procedures but have a have a poor understanding of the underlying quality principles. This can mean that changes required to implement improvements can be difficult to put in place in laboratories where the focus and training are weighted on following procedures, rather than on applying the underlying compliance principles. Additionally, when thinking "outside of the procedures" is required (such as when a quality deviation occurs), there can be an increased risk that the deviation is not well investigated/documented and that the potential consequences might not be fully appreciated.

Take something as apparently simple as documenting that an instrument is suitable for its intended use. In one industry, the combination of instrument and application may be treated as a "Black Box" or "Analyzer." In a different setting, the instrument might be part of an ISO 17025-accredited method. Typically in the pharmaceutical industry, independent consideration is often applied to the training of the analyst, the qualification (compliance) of the instrument, the validation of the method, the validation of the software or the integrity of the data. The language and processes used in the pharmaceutical industry are often viewed with caution by other industries. For example, discuss instrument compliance with an ISO 17025-accredited laboratory in terms of "operational qualification" and a typical response might be, "We are not a pharmaceutical laboratory and we don't need to follow their approach." Rephrase the question and ask if the laboratory would be interested in the principle of restoring and testing the accredited method as part of reducing the overall instrument down time before handing it back to the laboratory after maintenance and repair and you may receive a different response. But use the "wrong" compliance language to describe something and, irrespective of the potential benefits to the laboratory, the approach may not even be considered.

Part of the uncertainty around instrument compliance relates to the lack of definitive guidance. For example, in the absence of strong regulatory compliance guidance, many large pharmaceutical organizations have adopted Good Automated Manufacturing Practice (GAMP) principles.[3] The *United States Pharmacopeia's* (*USP*) general chapter on Analytical



Instrument Qualification <1058>[4] follows a different categorization process than GAMP on laboratory compliance. Both implement risk-based thinking by categorization, but GAMP is historically based on software, while USP <1058> is based on the calibration requirements and complexity/usage of the instrument. One problem is that when the FDA first implemented its guidance for pharmaceutical manufacturing validation in May 1987[5] many organizations applied the principles to laboratory instrumentation.

Unfortunately, the process validation principles defined in Ref. 5 were interpreted and diversely applied to laboratory instruments by pharmaceutical companies, instrument manufacturers and consultants. In many laboratories, this has resulted in poor understanding of what is required to implement new instruments, which can delay return on investment of result in compliance risks.

The fundamental importance of laboratory compliance means that it must be a core strategic priority for laboratory management. However, it is not uncommon for day-to-day job pressures and business priorities to limit strategic compliance thinking to being reactive, rather than proactive; this leads to those instances in which "inspection readiness" is not a strategic priority, but the work done just before the audit.

References

1. Smith, P.A. Strategies for successful analytical technology transfer. *Int. Pharm. Ind.* Winter **2013** *5*(4).
2. Federal Food, Drug, and Cosmetic Act (FD&C Act); http://www.fda.gov/regulatoryinformation/legislation/FederalFoodDrugandCosmeticActFDCAct/default.htm; accessed Feb 2015.
3. GAMP® 5. A Risk-Based Approach to Compliant GxP Computerized Systems; http://www.ispe.org/gamp-5.
4. USP General Chapter <1058> Analytical Instrument Qualification.
5. FDA Guidance for Industry—Guidelines on General Principles of Process Validation, May 1987.

Paul Smith is Global Strategic Compliance Program Manager at Agilent Technologies and has been working in laboratory compliance consultancy for the last 12 years. Within his Agilent role, Paul works with laboratories and organizations across a range of industries, as well as monitoring and sharing laboratory compliance trends across those industries. Prior to his compliance consultancy work, Paul worked in a variety of quality, management and analytical roles over 17 years in the pharmaceutical industry.