

Taming the Regulatory Beast: Regulation versus Functionalism

Michael P. Balogh and Virginia L. Corbin, Waters Corp., Milford, Massachusetts, USA.

Mass spectrometrists working in pharmaceutical development tend to approach the issue of regulatory compliance with some trepidation. We know we can't escape its considerable demands for our time and attention, and we're willing to act accordingly to ensure that our instruments and procedures comply. Yet it often appears that requirements are expanding in both scope and detail. This month's co-author succinctly sums up the issue: "The FDA wants to see quality built into the product at the beginning of the development cycle because quality cannot be ascertained at the end."

There are two schools of thought that conflict over what constitutes effective regulatory compliance. One abides by the methods FDA favoured for many years. The other prefers a retrenched view, one more closely informed by the original objective of ensuring good scientific practice. The debate's highly technical and quasilegalistic substance can prove challenging to follow sometimes.

A Brief History of GLPs and cGMPs

In 1975, the US Food and Drug Administration (FDA) faced an apparent failure of good science when it identified serious flaws in a non-clinical toxicological safety study.¹ The study had been submitted in support of applications to market new drugs and food additives. These were among the problems FDA cited:

- insufficient and poorly trained staff
- inadequate planning and supervision of work
- lack of personal accountability regarding materials used
- incomplete methodology
- reporting of findings for which no records existed.

Moreover, these revelations did not suggest an anomalous case. They did, however, point to a characteristic absence of control, responsibility, and in some instances, the commission of fraud.

This incident, which uncovered practices that could have endangered lives, led to the drafting of 21 CFR Part 58, the federal regulation known as good laboratory practices (GLPs). Forms of GLP had existed

in countries like New Zealand and Denmark since the early 1970s, but they were neither codified nor strictly applied. It wasn't until June 1979 that GLPs were finally compiled into a definitive source and given the force of law in the United States.

GLP, sometimes more broadly stated as GxP (where "x" can mean clinical, laboratory, manufacturing, pharmaceutical and so forth), describes the process and conditions that support the planning, performance, monitoring, recording and reporting of laboratory studies. Thus, the purpose of GLPs is to design and establish systems and procedures that ensure the high quality, integrity and validity of data generated during the testing of pharmaceuticals, food additives, cosmetics, pesticides and explosives.

Good manufacturing practices (GMPs), now called current GMPs (cGMPs), predate the GLPs and the evolution of quality control practices in pharmaceutical manufacturing. The basic tenet of the drug cGMPs, codified in 21 CFR 210 and 211, is that pharmaceutical firms must maintain appropriate documentation to support their various manufacturing and control operations.

Many aspects of regulation, such as a facility's suitability to accommodate analytical work, warrant examination but exceed the scope of this column. Even such fundamental issues as specifications for documentation standards and quality are not specifically noted in current regulations but are left to common sense. Though documentation standards do apply in some jurisdictions — the UK's Medicines Control

Agency, for example, includes them in its "Orange guide" — their adoption is by no means universal. For the most part, scientists must rely on little else besides common sense when determining the extent and adequacy of documentation.

In its emerging role as the primary analytical tool of drug discovery, mass spectrometry (MS) is increasingly subject to escalating regulation. A manuscript recently released by an industry workgroup captures the current state of regulation in the pharmaceutical industry, a time when relatively few distinctions are made on the basis of instrument type. The workgroup stresses holistic, common-sense regulation of analytical practice. The document "Qualification of Analytical Instruments for Use in the Pharmaceutical Industry: A Scientific Approach" appears on the American Association of Pharmaceutical Scientists (AAPS) website (<http://www.aapspharmstech.org>) and is written in a clear enough fashion to be useful for those less inclined to remain well informed of regulatory matters.² For those whose interest in regulatory issues runs deeper, a standing column that appears in *American Pharmaceutical Review* magazine and titled, quite transparently, "21 CFR Part 11," features a variety of experts from the pharmaceutical industry.

Pharmaceutical cGMPs for the 21st Century

The drug cGMPs have gone unchanged for more than a quarter of a century, a situation that is about to change. Having

evaluated its cGMP programme, the FDA will soon alter it, adopting a risk-based approach that ensures its regulations comprehend technological advances in pharmaceutical science and manufacturing technology. The agency wants to see quality built into the product at the beginning of the development cycle because quality cannot be ascertained at the end. The new, presumably more efficient, risk-based programme should encourage firms to develop their own risk-based approach, one that brings limited resources to bear on the most significant quality issues (that is, those with high public health risk). Moreover, FDA wants its new programme to stimulate innovation, particularly in the form of adopting new manufacturing technologies.

FDA has pursued the risk-based programme for a year and has made significant progress. Its site (www.fda.gov/cder/gmp) offers the latest updates regarding the 21st century cGMPs. So far, the agency has clarified the scope and application of 21 CFR Part 11, issuing the final guidance for industry: "Part 11, Electronic Records, Electronic Signatures — Scope and Application." It has also sent four proposed guidance documents to the pharmaceutical industry for draft review and is currently awaiting feedback. Finally, the FDA enforces violations of the regulations: product recalls, seizures, injunctions, consent decrees and arrest and prosecution by the agency's Office of Criminal Investigations.

The complexities and detail-driven nature of work in a regulated industry sometimes occludes a crucial point. Generally, companies want to "do" good science and produce quality data. We can apply the principles of risk analysis by evaluating operations, procedures and methods in which the potential for greatest harm to the public exists. Indeed, good scientific practice lets us minimize error and, where it does occur, identify it more quickly.

Mass Spectrometers Must Serve Their Intended Purpose

As a policy matter, FDA must inform industry of its requirements, which apply equally to regulated bioanalysis and well-characterized biopharmaceuticals and traditional pharmaceutical industry products. Compliance with the requirements must be documented and the records retained pursuant to 21 CFR 211.180. But the requirements don't distinguish among the various types of detectors, systems and methods used in

We can apply the principles of risk analysis by evaluating operations, procedures and methods in which the potential for greatest harm to the public exists. Indeed, good scientific practice lets us minimize error and, where it does occur, identify it more quickly.

analytical laboratories, nor do they state what companies need to do to achieve compliance with them.

Current regulations (21 CFR 211) address mass spectrometers and their use. Though the instruments do not require special testing, they must be properly calibrated and maintained — demonstrably fit for their intended use (21 CFR 211.67). The regulations also specify that only qualified personnel perform the work (21 CFR 211.25), that they use appropriately designed equipment and software (21 CFR 211.63) and that all operations take place inside a suitable facility (21 CFR 211.42 - 211.58). As for the operating software, it must be subject to a suitable change control and, like the instruments, properly calibrated and maintained (21 CFR 211.68). Finally, personnel must follow documented procedures, based on sound science, that ensure the quality and integrity of data they rely on when releasing a product from manufacturing (21 CFR 211.160).

To ensure compliance with the new regulations, you should select a mass-spectrometer manufacturer who understands the regulations and the intent behind their creation. Yet even then, you're likely to encounter compliance problems. The rapidly burgeoning body of regulatory legislation can bewilder anyone. But the extent and rate of regulatory growth is only part of the problem. The other, unfortunately, is us.

As well-meaning but independent thinkers, we will likely disagree about how to best interpret and satisfy the newly published regulations. So as we move to satisfy each new requirement, we might find ourselves debating which of its endlessly varied constructions to adopt. However unwittingly, we would free our own version of the Hydra, the mythical beast whose multiple snake-like heads spontaneously regenerated — in triplicate — each time Hercules lopped one off.

Coping with the Effects of Legislated Science

We are used to "doing good science"

simply because it is intellectually honest. Unfortunately, ethical motivation alone, proved inadequate. So good science is now legislated, and the consequence for us scientists is that we must deal with the Hydra.

The dictates of good science, of course, remain unchanged. Ensuring compliance must still include the various forms of qualification: installation, operational, performance, maintenance, method and calibration. But does achieving a goal of doing good science mean we must create great volumes of paperwork? The regulations merely require fitness for use, not perfection. Are we adding heads to the regulation monster for fear that we *might* not pass an inspection? Or should we instead base business decisions on risk analysis and best practice?

The most important part of any programme lies in the abilities of its participants. Because experience and business cards don't necessarily imply one's ability, the regulations require training for personnel performing the work and also for their supervisors (21 CFR 58.29 and 211.25). Moreover, the training requirement extends to hired consultants, who must be satisfactorily qualified and able to provide documented evidence of their qualifications (21 CFR 211.34).

A manufacturer should offer training and education for users of its instruments and software. It should also be able to offer documentary evidence that its trainers are certified professionals who must renew their certifications regularly. Proper training and qualification ensures that competent people are authorized to perform their jobs, and it minimizes the extent of human error.

Sometimes the manufacturer offers minimal information on its website and more detailed information via links to other, unaffiliated groups or services. For example, Agilent's site (www.chem.agilent.com) addresses five primary areas of concern but for more technically sophisticated issues, it links a more extensive site (www.labcompliance.com). Similarly, Waters offers support and value-added service through the Connections University

MS in Practice

(www.waters.com) and provides links to specialized validation services (www.taratec.com).

Mass spectrometer manufacturers producing compliant-ready products offer suitably designed equipment and applications software. This means the products are properly designed (21 CFR 211.63 and 58.61) or structurally validated. Proper design of mass spectrometers and their operating software signifies that quality is built in at the beginning of the product life cycle using a defined, documented process reviewable during an on-site audit. Afterward, the instrument and its software must be installed according to the manufacturer's specifications, calibrated and maintained (21 CFR 211.67 and 211.68), and records of those actions retained as specified in 21 CFR 211.180 and 211.182.

Before regulated users run their final performance qualification to demonstrate a system is fit for intended use (21 CFR 211.67 and 211.68, 21 CFR 58.63), manufacturers must provide them with qualification procedures (installation, operational, performance and maintenance) as evidence that the system performs according to its specifications. The phrase "fit for intended use" also means that the user has performed method validation (21 CFR 211.160) on the mass detector, verifying that it meets documented requirements for linearity, accuracy, precision and the other parameters defined in the regulations and guidance documents. Significantly, users should not construe "fit for intended use" to mean that they must perform a complete design verification. Indeed, they need only apply a risk analysis to identify which instrument and software functions they must test in their environments before they can use the system for commercial production or release a product.

Using mass detection in a regulated environment requires a good relationship with the instrument's manufacturer, an understanding of the regulations, and implementation of good scientific practice in the laboratory. If your laboratory already conscientiously observes good scientific practice by following documented protocols and protecting the integrity of acquired system data, you are well-poised to meet the regulatory requirements. Ultimately, it is not about how much documentation you produce but producing the documentation that proves you can meet the intent of the regulations consistently. Risk analysis can save you

from adding extra work to an already intense situation and help you defeat the regulations Hydra. Compliance should not add more heads to the beast but should instead present a way to tame it.

References

1. K. Robinson, *BioPharm Int.*, August 2003, 38–46.
2. S.K. Bansal et al., *AAPS PharmSciTech.*, 5(1), (2004).

"MS in Practice" editor **Michael P. Balogh** is principal scientist, LC-MS technology development at Waters Corp. (Milford, Massachusetts, USA); an adjunct professor and visiting scientist at Roger Williams University (Bristol, Rhode Island, USA); and a member of LC•GC Europe's Editorial Advisory Board. Direct correspondence about this column to: "MS in Practice", LC•GC Europe, Advanstar House, Park West, Sealand Road, Chester CH1 4RN, UK, or e-mail: dhills@advanstar.com

Virginia L. Corbin is Manager of Corporate Compliance Marketing at Waters Corp. (Milford, Massachusetts, USA). She is responsible for the worldwide FDA compliance programme and also for compliance of Empower and MassLynx software products for the regulated industry.

Virginia earned her Bachelor of Science in Organic Chemistry from Stanford University in Palo Alto, California, USA. She has been employed at Waters since 1988 and in her role there has been responsible for cGMP compliance, and has been the Corporation's interface with the FDA on new regulations affecting the software industry. Prior to her current position, Virginia also served as Director of Regulatory Affairs at Waters and coordinated the ISO 9001/TickIT certification for software development and design. She had 25 years of experience as a chemist, lab manager and software evaluator in the pharmaceutical industry prior to joining the company. Ms Corbin is an invited speaker and has lectured extensively on compliance issues at various technical symposia around the world.