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QUALITY RESOURCES



Minimizing Risk in Complex Biotech Environments

Introduction

Risks in biotech companies span all levels of the organization. From business risk – more intense in a young industry, to research risk – whether the treatment will work as promised. Unique to the life science industries are the regulatory risks, which are more intense in biotech because of the greater scrutiny the FDA applies to these companies. As part of the regulatory pressure, a company must prove that their assets (instruments, production equipment, etc.) are properly managed, including calibration, maintenance and validation.

Developing regulatory asset management systems and procedures to contain these risks and enjoy the inherent productivity benefits of well-managed assets can be challenging given the severe resource constraints of growing biotech companies. This pressure is even greater for those who are charged with getting all new systems up and running at a new site.

While evaluating potential systems, it is important to keep in mind that because of the higher number of instruments with tight tolerances at biotech companies and the greater attention given to calibration by the FDA, the management of the calibrations of assets usually poses a greater regulatory risk than general maintenance. Your regulatory asset management system, whether it is a combination of systems or single integrated system, should therefore provide best-in-class calibration management to minimize that risk.

Calibration Risks

The importance of careful calibration management is made evident by the nature of risks that derive from poor calibration management. During research, for example, there are certain scientific risks associated with calibration. Most scientific data comes from measurement, and to draw the proper conclusions and maintain control over experiments, it is important to have confidence in the data registered by your laboratory instruments. However given the ever-present Second Law of Thermodynamics, these instruments will tend to offer less and less accurate data if left un-calibrated. In order to maintain confidence in these instruments they need to be calibrated on a regular schedule and in order to determine the optimal interval for that calibration, it is useful to have easily analyzable documentation of the calibration details for each instrument – including calibration date, pass/fail, and “as found” (measurements taken immediately before calibration). If an issue with a particular instrument does arise, it is also useful to have a traceable history. This history can then be used to determine which batches of product that instrument could have impacted. In some cases too that instrument may serve as a standard for other instruments, in which case there should be a way to determine which instruments would be impacted by that standard.

Another example of a risk that derives from poor calibration management would be regulatory risk. Once the treatment has been introduced to humans, government agencies (i.e. the FDA for treatments distributed in the United States), require evidence that the product is being produced within documented tolerances. They therefore are looking to establish confidence that the instruments and equipment are operating in a controlled state. Therefore calibration is featured in many of the regulations and comes up regularly in citations. For the United States, these regulations include:

- 21 CFR Part 58: Good Laboratory Practices (GLP)
- 21 CFR Part 211: Good Manufacturing Practices (GMP) for pharmaceuticals
- 21 CFR Part 606: Good Manufacturing Practices (GMP) for biologics
- 21 CFR Part 820: Quality Systems Regulations

Because these regulations are in place in order to assure the public of product safety and efficacy, these government organizations are more concerned about, and therefore apply more scrutiny to, the accuracy of instruments and equipment than they are with the maintaining of equipment in a productive state.

Both the scientific risks and the regulatory risks spawn significant business risks, so much greater in the biotech industry because of the large investment in intellectual property and product development. In the research phase,

misleading measurements can provide a real setback and have a noticeable impact on morale as researchers become frustrated when results are not as expected or are difficult to reproduce. Expansions to the research phase naturally then imply greater investment and a slower return on existing investment.

As a business begins clinical trials the stakes clearly go up, not only because of product safety concerns and the significant amount of investment at stake by that point, but also because of the public relations implications of problems at this stage, affecting both ultimate product acceptance and immediate potential for finding new investors. With the government agencies now applying scrutiny to the process, the risks are not only to failed or irreproducible trials, but also the risk of citation or shutdown for regulatory violations for poor calibration management. Good practices in this phase are an important foundation as a company scales up to full production after successful trials. With a strong foundation and experience with disciplined calibration management, the risks of failing to achieve government approval for production are significantly reduced, certainly one of the most stressful times for a growing biotech company.

Once in production, while marketing the product, the business implications of regulatory risk really kick in. A regulatory citation for violation of calibration management requirements might not only cause serious inconveniences in the short-term, but since regulatory agencies will often audit companies with a history of violations more often it could also lead to greater scrutiny and inconveniences in the future. Also, at the most extreme, government agencies can put on hold or shut down production entirely with obvious and most serious business impact.

Complex Biotech Environments

There are several unique characteristics of biotech organizations that complicate the management of calibration, as compared with traditional pharmaceutical companies. First, there is the simple volume and nature of instruments used in biotech research and production. Depending on the current phase, there are general laboratory instruments (such as pipettes, balances, thermometers, and timers), analytical instruments (such as LC and GC, mass spectrometers, sequencers, and micro array technology), and process instrumentations (for measuring temperature, pressure, flow, humidity, dissolved oxygen, pH, and conductivity).

When the total number of instruments is small, and when the responsibility of managing the instruments is limited to a single individual, maintaining disciplined calibration is fairly straightforward. However, with the introduction of a broader range of types and numbers of instruments and increases to the number of people who enter or access calibration information (calibration technicians, managers, etc.), keeping all the unique calibration procedures, schedules, and tolerances straight can be quite daunting without a more sophisticated calibration management system.

While lean manufacturing is a common practice today, the limited resources in the biotech industry are generally at a whole different level because of the startup nature of these companies. They are working with a limited number of people, each with his or her unique area of expertise where they provide the greatest value to the organization. Implementing and validating new systems means taking someone away from what they do best, slowing down development in other areas.

With the large investments, anxious investors, and the urgent needs for the treatments biotech organizations are working on, most biotech organizations are on very aggressive timelines, constantly under pressure to further shorten the time to market. That means doing multiple projects at once and doing them right the first time to avoid having to take time to fix mistakes with the government watching. Managing those multiple projects with the discipline and precision required, and with the limited resources mentioned above, is a headache in a scale unique to biotech companies.

Added to the stress of aggressive timelines, is the fact that most biotech production facilities are brand new sites. In most cases, the type of production that is done in biotech is sufficiently different that even if adapting an

existing site the multitude and variety of projects that need attention is daunting. However, the good news is that a new site allows biotech companies to implement “best-in-class” solutions without concern for legacy systems.

Minimizing Risks

With the risks associated with calibration outlined above, it is clear that careful consideration should be given to a solid Calibration Master Plan to minimize those risks. A complete inventory of all instruments should be made and maintained, along with the calibration procedures, tolerances, and standards to be used for each instrument. The plan should include provisions for keeping a history of all calibrations, including date of calibration, pass/fail, measurement data (before and after calibration), and standard used. With these records the company not only satisfies government regulations, but also has the data to perform interval analysis, to find the optimal schedule for calibrations, and is able to trace backward all instruments that used a standard that has become unreliable.

To manage the schedules, record the histories, and afford the opportunity for reverse standard traceability, some sort of Calibration Management System will be required. For small start-up biotech organizations, this might simply be a simple paper, Microsoft Excel, or Microsoft Access system. However, these systems quickly prove inadequate as the company enters new stages in their development.

A more sophisticated system will be required when companies add more instruments and more calibration technicians. The system will need to have all the standard features: be able to track an unlimited number of instruments; collect, store, and analyze measurement data before and after calibration; provide immediate notification of instruments that fail calibration or are found out of tolerance; allow reverse traceability of standards used in calibration, and keep an audit trail (with electronic signatures if using a paperless system) for changes made to instrument records.

The real test for a system, however, will be how well it fits your unique needs. It is important to determine how flexible the system is for collecting the information you need to collect in the order that makes the most sense for your procedures. Some systems will allow you to customize the fields to create the field labels and types in the order you need them, while concealing fields you don’t need or use. This customization should be straightforward and not require any advanced skills. The system should also be flexible enough to satisfy your existing security procedures for passwords and access control.

When evaluating systems it is easy to focus almost exclusively on the features of the packages under consideration. However just as important is how the critical features are implemented and how easy or difficult the software is to use. Bringing new users up to speed on a new system will naturally be easier the less difficult the software is to use, just as the time spent interacting with the software will be less if it can be catered and streamlined to your needs. One key area of concern would be how easy it is to enter calibration measurement data for a wide variety of instruments, with a wide variety of data types and tolerances. Such a regular task cannot be tedious.

The system should also be based on a robust technical platform that will grow with your organization as you add new users and new sites. To extend the useful life of the software and to accommodate growth, the system should take advantage of the power and reliability of new established technologies. Clearly with the risks involved your business is not the place to experiment with the cutting edge technologies, however the benefits of established and proven technologies can be quite compelling, including lower costs of installation and maintenance, lower bandwidth requirements, and greater stability.

With limited resources, managing the calibration management system life cycle can be a significant challenge. Rarely does it make sense to hire someone who is an expert in these lifecycle steps, but at the same time it is often equally difficult to take someone off their current tasks. The typical system lifecycle would include the development of the system requirements, which comes from the Master Plan; the software selection, including a comparison of the user requirements specifications versus the functional specifications of the software; software implementation and training; software validation; data migration from any previous system, if upgrading from a simpler system to a full calibration management system; and system optimization after the system has been running to uncover additional benefits and increase return on investment.

To overcome the internal resource constraints, and to ensure that the job is done right the first time, many biotech firms are outsourcing some or all of the steps in the development of calibration system and processes. By working with an outside firm who has experience with calibration management, biotech companies can acquire the focused expertise without the difficulties of hiring someone for the project themselves. This outsourcing could go so far as to include an entire turnkey calibration department, including much of the Master Plan, SOPs, and software implementation and validation. With a trusted, experienced partner a biotech company can significantly reduce its risks of being out of compliance, enjoy more of the benefits of a calibration management software system, and get up and running quicker, often at a lower total cost than if they did it on their own.

Conclusion

Controlling risks associated with calibration is not, in principle, a difficult task. However given the large number of instruments, limited resources, aggressive timelines, and high expectations at most biotech companies, it is also hardly something to take lightly. The right calibration management system, one designed to satisfy the unique requirements of regulated life science companies, can greatly simplify the process and reduce regulatory, scientific, and business risks. The challenge, however, is implementing such a system without disrupting ongoing projects in the process. The solution to this challenge for many biotech organizations is outsourcing all or part of the development of their complete calibration system and processes.

About Blue Mountain Quality Resources

Blue Mountain Quality Resources has 15 years of experience implementing calibration management systems for biotech and regulated life science manufacturing companies. The company's own calibration management system, Calibration Manager®, with many features designed specifically to meet the rigorous demands of biotech companies, has been installed in over 1500 companies, with over 50 implementations at biotech companies, including Baxter BioScience, Imclone Systems, Wyeth Biopharma, Biogen Idec, and MedImmune.

Their suite of implementation services, available individually or as part of complete solutions, was specifically designed to leverage their experience toward reducing costs and risks in implementing and validating these systems. Their consulting services, offered by individuals with years of experience directly in calibration at biotech companies, provide these companies with a solution for getting a compliant and efficient calibration department up and running in the required timeframes.

For more information about how Blue Mountain Quality Resources can help you contain your calibration risks visit www.coolblue.com, email us at biotech@coolblue.com or call 800-982-2388.