Original Article

Bottom line compliance for biotechnology: Six secrets

Received (in revised form): 8th December 2008

John Avellanet
is a leading authority on simplifying and streamlining regulatory compliance and quality systems, coaching executives in effective compliance programs and helping bring new medicines to market faster, easier, for less. He specializes in serving small to midsize companies, and can be directly reached through his independent consultancy, Cerulean Associates LLC at john@ceruleanllc.com.

ABSTRACT **Biotechnology executives frequently short-shrift one of the key indicators of return on investment when negotiating pharmaceutical partnerships, support or licensing: a compliance and quality system. Given the increasingly tight financial markets biotechnology executives must operate within, can a good quality system be established for less than the cost of an average car?**

Journal of Commercial Biotechnology (2009) **15,** 251–256. doi:10.1057/jcb.2008.60; published online 3 March 2009

Keywords: compliance; regulatory; quality systems; FDA; biotechnology; pharmaceutical

INTRODUCTION

The biggest barrier to quality systems compliance among small and startup biotechnology companies is money. And yet, for prospective pharmaceutical partners, a biotech firm with a quality systems program will always demand a higher price than a biotech firm that has ignored even the basics of regulatory compliance. The reason: the less re-work a pharmaceutical company will have to undertake after signing a deal with a biotechnology firm, the more leverage the biotech firm will have in negotiation. At the negotiating stage, perceived potential re-work is driven by pharma's understanding of how much of a biotech's lab results and preclinical testing occurred under a quality system.

Ironically, in my work advising and coaching executives on how to get the most powerful results in their compliance and quality systems with limited resources, few of the members of my SmarterCompliance program know how much of their budget to devote to quality systems and regulatory compliance. Even in large and midsized companies, this uncertainty exists – a 2006 study of executives revealed that 35 per cent of the respondents remain in the dark as to how much of their budgets should be tied to compliance-related activities.[1]

Clearly then, attempts to budget for compliance and quality systems in small and startup biotechs are hampered by uncertainty as to reasonable baseline costs. Although there is no 'right' answer, in the past, I have set the new members of my SmarterCompliance program a challenge: How would you establish a good quality systems and compliance program for less than the cost of the average car (for example, $25 000 in the United States)?

There are many ways to achieve this head start on lean compliance, but for the

Correspondence: John Avellanet
Cerulean Associates LLC, PO Box 498, Williamsburg, Virginia 23187-0498, USA

management team leading a small or startup biotechnology firm, six crucial steps will help you work your way into a smarter, leaner compliance posture.

ONE: LINK COMPLIANCE TO BUSINESS STRATEGY

Forget all the preaching you might have heard, seen or read on how good compliance and quality are really just good business practices. Look back at the 'Introduction' section of this paper. The link I use is simple: the better your compliance maturity, the stronger your negotiating hand.

The cost of non-compliance to you and your company, not to mention your inevitable patient, is significant. And, at least in the United States, biotechnology executives also need to worry about the rise in investor lawsuits aimed at executives whose actions – or inactions – have delayed product approvals, led to poor-performing partnerships, or otherwise negatively impacted the bottom line. Biotech management cannot be passive when it comes to compliance. Executives need to support the initiation and development of a quality system.

Whether that support comes from a fear of personal liability or a worry about losing a negotiating card, management must communicate to all biotech employees the link between compliance and business strategy. This is the first secret: ensure you and your employees are clear on the bottom line.

TWO: DEFINE YOUR OVERALL COMPLIANCE FRAMEWORK

As a biotech executive, insist on the development of a quality plan or framework. Many consultants and quality experts will help you put together a detailed plan for you, with resource levelling, timing and dependencies. Do not do this.

Big plans entail big expenditures. Given the key obstacle – money – to establishing a functional quality system and our challenge limit of US$25 000, this traditional approach is a luxury we cannot initially afford.

Instead, make do with what you already have. Now many executives I work with are a bit uncertain at first what this means until I pull out the tool they already have: their org chart. Your companies organisation chart is a visual framework that can do double-duty as a tool to put together a compliance plan in five steps:

1. Replace the typical personnel titles with standard operating procedure (SOP) titles;
2. Group these into 'departments' or functional areas (consider adopting something akin to the US Food and Drug Administration's breakdown of modern quality systems into seven groups: management, laboratory or design controls, production and processes, records management and change control, facilities and equipment, and continual improvement and corrective and preventative actions)[2];
3. Tie everything together up to an overarching quality policy (for example, in the slot for president of the company);
4. Connect the quality policy to a set of guiding ethical principles or a code of conduct (consider this the company 'board of directors'); and
5. Over time, shade in or otherwise distinguish the boxes as you complete them.

The result should look like Figure 1.

You can find more detail on how to go about this in the presentation I gave this past October, 'Effective Oversight of Compliance and Quality Systems for Senior Executives – SOP and Policy Oversight' (see the recorded version at http://www.ceruleanllc.com/seminars).

Many of the SOPs and policies you will eventually create will dependent on your specific company and its operational environment (for example, privacy must be addressed in the European Union, less so in the United States or elsewhere). The key is to keep your plan simple, structured and

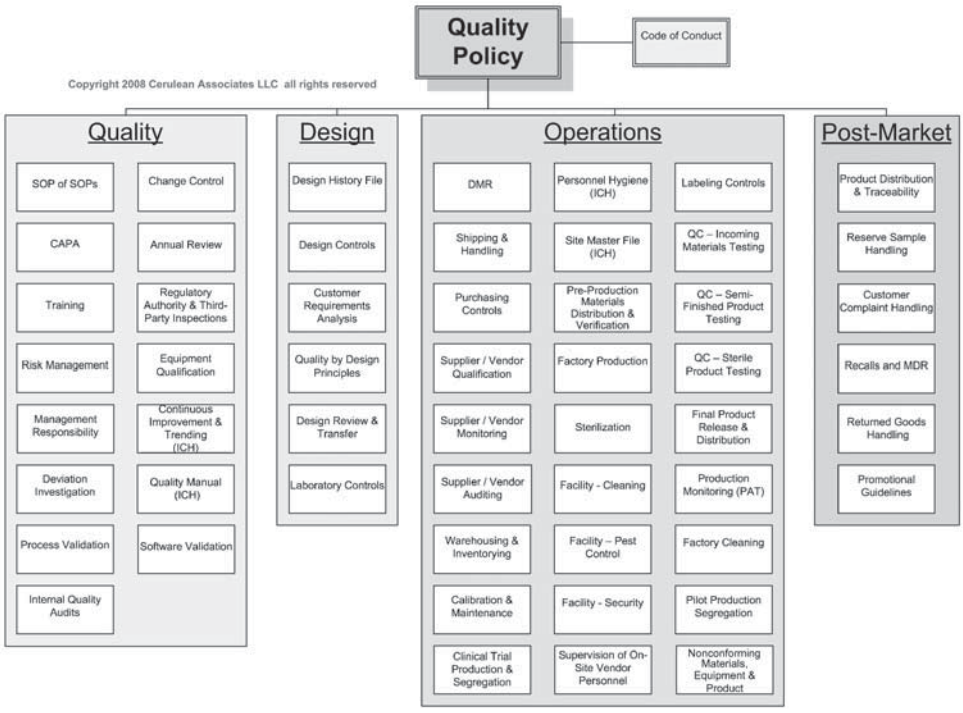

Figure 1: Sample quality systems plan.

straightforward, and the secret is using a tool you already have on hand.

THREE: MAKE CREATIVE USE OF OUTSIDE EXPERTISE

When executives envision 'outside experts', consultants come to mind. Given our lean approach and challenge limit, however, traditional consultants – particularly those in large consulting firms charging $30 000 to $40 000 for a simple, high-level industry best practices report – are outside the scope of our budget. Creativity is called for.

Reading this paper is one example of creative use of outside experts. Does the paper have all the answers you need? No, of course not. Does it help to put in place one or two pieces of the puzzle? Yes. Reviewing the recorded presentation I referenced above with your team can add at least two more pieces. What next?

More article reviews and more recorded seminars are available online to help you fill in more gaps, but over time, this can be a costly way to go. I have seen 1 hour on-line training courses that cost upwards of $500 for a set of PowerPoint slides and running commentary; that is more than the cost of an hourly consulting fee. So while article reprints and recorded seminars are a good short-term option to jumpstart your compliance, solve a thorny problem or fill in knowledge gaps, solely relying on articles and seminars will not complete the puzzle and keep us under our budget.

This leads to the next creative tact: turn the traditional approach to building a quality system on its head. The typical strategy is to put in the compliance system, conduct an internal audit or two, and then look to hire an independent consultant to conduct a mock FDA audit or gap analysis. Creative use of outside expertise calls for the opposite tact – get the audit now. Just make sure to have completed at least a few steps – communicating the compliance – business

linkage, drawing up a quality plan, and perhaps writing a policy or two) – before you seek out a mock FDA audit.

Now, a waste of money and time would be to ask for the normal mock FDA audit. Given that were turning the process on its head, go all the way: ask for a non-detailed audit. You want a high-level mock FDA audit with a set of prioritised recommendations and the underlying logic. Many of the specific gaps the independent consultant will find are irrelevant – as a small growing biotech, your company's strengths and weaknesses are fluid; this afternoon's gap may be filled simply by coincidence with a new hire tomorrow morning. Remember: You only want a handful of prioritised recommendations specific to your business, the reasons why, and the associated best practices for those areas. You do not need the best auditor or the most detailed 200+ page audit.

You need this high-level mock FDA audit and report to help you stay lean and stay reasonable. First, because this is not your usual 3- or 4-day on-site audit (confine it to 1 or 2 days on-site), your costs will be less. Second, the report's prioritised recommendations will inevitably be based on a mix of your specific company challenges plus the outside expert's insight into how to apply his/her knowledge and industry best practices to your specific situation. In essence, you are getting two birds with one stone: an expert report plus a proposed set of priorities drawn from your original quality plan.

As to keeping the cost low, you need to negotiate for what you want and that will entail either brilliant negotiation on your part or, more realistically, knowing what a reasonable fee range for this type of audit and report. Recall our $25 000 budget. Expect this audit and report to be our most expensive expenditure – one we will make good use of for the next year or two at least – so let us set a broad ballpark estimate of anywhere between 25 and 70 per cent of our budget, or between $6250 and $17 500 – including travel costs.

Now, let us refine this a bit more. With some consistent digging, wonderful information can be found online in the EU's various websites and documents. Earlier this year, I stumbled across a 2006 guidance document for certifying entities that cited a typical audit cost between €5000 and €8000 ($6300 and $11 000). My suggestion is to budget something on the higher end of the range to allow for the slightly different twist we are putting on the audit and the report (this will limit the consultant's ability to use a canned report – he or she will need to do some thinking on our behalf). Add in an estimated travel cost plus a bit of a buffer for any 'unknown-unknowns' (30–35 per cent) and we have a total budget estimate of $8500 to $15 000.

With this budget range in mind, when you talk to various independent consultants, anyone who gives you a preliminary quote of more than our top range can be quickly eliminated. More tips on finding the right independent consultant for your company to conduct this mock FDA audit and prioritised report (or any other activity) is outside the scope of this paper, but you can read a fairly detailed process reprinted from 'Getting Results You Expect from Consultants'[3] posted here: http://www.ceruleanllc.com/Resources/Choose_a_Consultant_Get_Results.htm.

FOUR: DRIVE RISK CONTROL INTO DAY-TO-DAY DECISIONS

Risk assessment and management can be a complicated process. A small or startup biotechnology firm does not have the luxury to learn complicated toolsets; chances are, you and your colleagues already have enough complexities in your day-to-day laboratory activities. Simplicity is the real secret here. If the financial meltdown of 2008 has shown anything, it is that complex risk methodology tools are no substitute for good judgment. Good judgment can come into play just as easily under a simple system as it can under complex modelling methods.

I have laid out a fairly simple, structured risk assessment and controls analysis process in several of my 'lean' articles and recorded seminars;[4] I will not repeat it here other than to emphasis the criticality of both you and your management team relying on a systematic approach that is straightforward enough to allow is regular and consistent usage in any business decision-making process. Whichever risk control process you decide on needs to not only define the risk but enable you to document proposed mitigation strategies.

The FDA requires many biologics makers to submit a risk evaluation and mitigation strategy (REMS) with new applications for market approval. Earlier this month, I reviewed a preliminary FDA REMS template for my SmarterCompliance Toolkit; the FDA's REMS template is eventually destined to be published in a publicly available guidance document. The template (at the time of writing) is brief – less than two pages in length – and has just four headings:

- Goals – the mitigation strategies for identified risks;
- Elements – monitoring plans, communication plan and documentation plans;
- Implementation – how the above will be implemented and monitored and
- Timetable – specific schedules of implementation and reviews.

Use this REMS approach inside your company when considering significant business decisions (such as projects to undertake). For instance, if a colleague suggests that a battery of toxicology tests be initiated at a contract research organisation, ask him or her to submit a two-page REMS as part of the project proposal; then ask the contract organisation – as part of its bid – to submit their own REMS. Occasionally, this may be an exercise in the obvious, but the internal importance is less about having a REMS for any given business initiative, and more about creating a culture used to documenting and thinking in terms of calculated risk-taking.

FIVE: BUILD IN COMPLIANCE AS YOU CAN

This does not mean implanting inflexible, rule-bound quality procedures more attune to a mature organisation, but rather to designing your processes and equipment to take advantage of available pre-configured compliance components. A simple example is buying SOP templates on-line and then tailoring them to your environment rather than writing from scratch. However, of far more criticality are the choices you make around equipment because of the long-term impact.

For instance, if you have the choice between purchasing (or otherwise using) laboratory data collection equipment such as laboratory information management systems (LIMs) or electronic laboratory notebook systems (ELNs) or high performance liquid chromatography systems (HPLCs) that are generic versus those that have an additional module for compliance with the electronic data integrity rules (the FDA's Part 11 or the EU's Annex 11), consider strongly the latter compliant version. This catch-as-catch-can approach is not ideal, but it is a good tactic to keep you lean and on track for that stronger negotiating hand. Assays conducted in accordance with good laboratory rules and data compliance are just the proof you need for any prospective pharma partner or licensor.

SIX: ESTABLISH AN ANNUAL COMPLIANCE REVIEW

As a small or startup biotechnology company, conducting the typical, detailed annual quality systems review espoused by the International Conference on Harmonisation guidance, ICH Q10 Pharmaceutical Quality System, is inappropriate. Your goal, at this stage, should be to establish a regular management check-in

that documents management involvement, support for, and interest in continual improvement of an effective compliance and quality system.

A few critical metrics – even something as simple as SOPs written versus trained on when you are starting out – plus a dashboard-like report or two can set the stage for next year's initiatives and priorities, and provide you the documented proof you need to show good executive oversight. Consider using the mock FDA audit and the independent consultant's original proposed priorities as a baseline. Or, if you are really in a crunch – financial or otherwise – use the audit report and its recommendations as the focus of your review: how have we done? What have been our challenges so far? What do we need to keep an eye on? In this way, you can make the audit and report serve an additional purpose beyond its original intent, increasing the results from your limited resources.

FINAL THOUGHTS

Compliance is not a zero sum game, but neither should it be a drag on your bottom line. Striking the right balance is a long-term challenge, but following these six practices will put you on the right footing.

Are you ready?

REFERENCES

1. BPM Forum. (2006) *Compliance Enabled Enterprise the Future: Building the Compliance-Enabled Enterprise*, CEO magazine and the IT Compliance Institute.
2. Quality Systems Inspections Reengineering, US Food and Drug Administration, September 2000, www.fda.gov/cdrh/gmp/gmp.html.
3. Avellanet, J. (2008) Getting the results you expect from consultants. *BioPharm International* 21(4): 32–36.
4. See my article (2008) Shared risk: A regulatory management strategy. *BioProcess International* 6(3): 20–25, March 2008, http://www.ceruleanllc.com/Articles/Default.htm, plus either my August 2008 'Managing Supplier Risk – FDA Expectations' or May 2008 'Lean Outsourcing and Supplier Selection,' www.ceruleanllc.com/seminars.