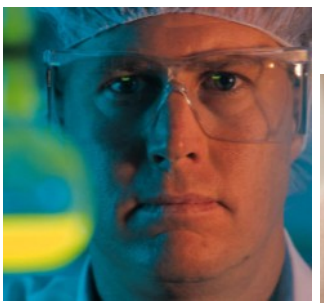
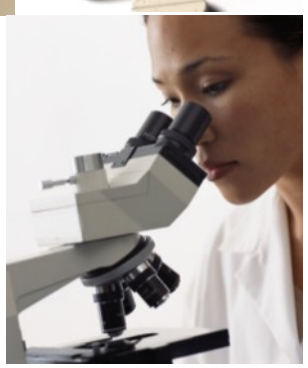
BY JOHN AVELLANET







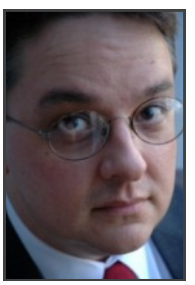


Is Quality by Design Right for My Organization…?

OR

Would I Prefer "Quality by Crisis"?

ABOUT THE AUTHOR:



John Avellanet is a successful business executive and advisor, an internationally recognized regulatory compliance expert for R&D environs, a dynamic public speaker, and the author of more than 20 internationally syndicated articles, co-author of the book, Best Practices in Biotechnology Business Development (Ingram and Baker & Taylor, publishers), and the publisher of the monthly executive newsletter, *SMARTERCOMPLIANCE*™. A repeat guest on business radio shows such as *Tomorrow's Business* and *My Technology Lawyer*, he is a frequent speaker at universities, businesses and industry trade associations.

Reprints and audio excerpts of many of John's published articles and interviews are on the Cerulean website (www.ceruleanllc.com).

In his workshops, John shares hard-hitting, practical information on:

- Cost-effective Lean Compliance
- Quality by Design
- Preventing intellectual property theft
- Simplifying records management and IT compliance

If you're interested in having John hold a workshop for your company, or would like to gain private access to his expertise, please call, write or visit:

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PRAISE FOR JOHN AVELLANET'S WORK:

"John is the most user-friendly Compliance and IT person I've met in 25 years and a true professional in every sense of the word. As far as I'm concerned, he is the best in the business. I consistently recommend him to my Senior Executive-level colleagues who need help with Regulatory Compliance, Intellectual Property or IT. "

— William Cope, President [*underlines in original letter*]
Pine Island, Florida

"Five years later and, in my opinion, the strategies John helped us build and put into place should be the model for anyone needing to enhance productivity while dealing with regulatory compliance."

— Timothy Beane, Vice President, Research & Development
Richmond, Virginia

"I have not encountered many people in this industry who share your pragmatic, methodology-agnostic, 'let's just do the right thing' approach."

— Gene Babinsky, Senior Manager, Product Development
Chicago, Illinois

"John has the ability to reduce complex concepts into terms that make sense to diverse audiences. He possesses the rare talent of being to handle sensitive issues in a direct and productive manner that promotes on-going dialogue and solutions."

— B. Nowak, Director, Business Intelligence
Grand Rapids, Michigan

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OR Would I Prefer Quality by Crisis?

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INTRODUCTION

This booklet is divided into three sections:

- **Is quality by design right for you and your company**? This section walks you through industry facts and statistics on the current costs, success rates and time involved for drug, biologic and medical device development. It answers the most common questions about if and how quality by design can—and cannot—help to lower costs, improve success and speed time to market approval.

- **Making an informed decision on external expertise**. This section covers questions you should answer *before* you make a decision about bringing in consultants.

- **Five tips for a "lean" quality by design blueprint**. A bonus section with five simple steps you can apply today speed time to market by *at least* 12%.

I recommend you review section one first; there is no need to continue if you determine that quality by design is not an appropriate strategy for you or your organization.

Quality by design for new product development is not as process-driven as quality and compliance in manufacturing; thus, I have seen a lot of executives struggle with quality by design. In its worst form, this confusion results in a significant waste of time, effort and money—assets that investors and shareholders are less and less willing to forgive.

CAN I WAIT TO IMPLEMENT QUALITY BY DESIGN?

By providing you with the facts you'll need, this booklet is designed to help you make an informed decision about whether to apply quality by design to your company's product development and design processes.

You can choose to sit this one out or you can choose to join with others who have seen how quality by design can speed their time to market by 50% with easier, faster regulatory approval.[1]

> *"Quality by design is going to be an evolution, but eventually, years down the road, the regulations will reflect what successful companies have done—those first through the quality by design gates."*
>
> - Dr. Janet Woodcock, Deputy Commissioner and Chief Medical Officer, US Food and Drug Administration.[2]

Notes:

The term "**lean**" (as in "lean quality by design") denotes a highly efficient, highly effective approach that makes the most of a company's internal knowledge and capabilities at the lowest cost. Toyota pioneered the concept of "lean" back in the 1970's for both its manufacturing and product development environments.

"**Quality by design**" (QbD) is part of the Food and Drug Administration's (FDA) good manufacturing practices for the 21st century. Prior to FDA adoption, quality by design was in widespread use through consumer products and software development to incorporate predefined product aspects (such as consumer preferences) as early as possible in the product design phase. This then established a product vision which served as a reference to arbitrate conflicting constraints and limit late stage changes.

The FDA has defined quality by design as "designing and developing a product and associated manufacturing processes that will be used during product development to ensure that the product consistently attains a predefined quality at the end of the manufacturing process."[3] In other words, incorporating predefined product quality aspects (such as safety and efficacy) during the pre-clinical product development stage to ensure the new drug, biologic or medical device meets these critical thresholds.

Under a QbD approach, by the end of Phase I clinical trials, your focus is on micro-refinements of the critical product attributes, optimizing manufacturing processes and using the remaining clinical trials as verification and validation.

The bottom line:

Faster time to market

and

Easier regulatory approval

DO YOU HAVE A RIGHT TO BE CONCERNED?

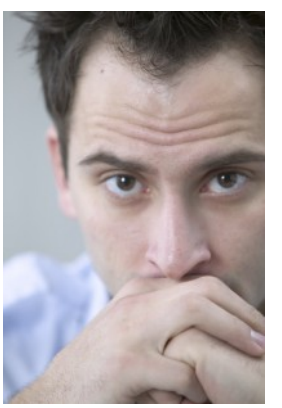
Before you can feel comfortable about tackling quality by design and improving your time to market speed, you must be convinced that the risk of needing to speed time to market is real. If you're not sure that you need faster creation, development and design of your new products combined with easier regulatory approval, take a look at the following statistics:

- The average time to market for new Food & Drug Administration (FDA) regulated products is now 10-15 years: 1-2 years for discovery plus 3-6 years for preclinical plus 3-6 years for clinical plus 1-2 years for review and approval.[4]
- The average cost to bring a new product to market has risen to $1.2 billion for drugs, medical devices and biologics.[5]
- Typical investment burn rate is $30-50 million per year.[6]
- Typical success rate of new innovations to marketplace approval is 250 to 1.[7]
- Of the successfully approved products, only 30% will recoup their investment costs.[8]

Our emotions get tied up in our work and may make us feel as though we can do better, that others made mistakes that we won't, and that our work is proceeding at a good rate. But, these statistics highlight the probability that any company can improve before time and resources give out.

Of course, none of us can ever know what tomorrow holds. We can only be sure that our new product will succeed, or won't. Speeding time to market is critical for those who worry about their new product success in the marketplace. That there might be risks on the long road ahead, including:

- Increased competition
- Patent breakage
- Generic versions
- Black box warning labels
- Intellectual property theft or loss
- Insurance or government mandated price points



For new pharmaceutical compounds alone, only 8% will reach the market.[9]

The real life expectancy of a patent today is less than 12 years.[10]

What do you believe your company's chances are of bringing your current project to market fruition? _____%

What are your chances of being able to recoup your development costs once your new product hits the market? _____%

If you wrote that your chances were 30% or less, you should continue to the next page. If you wrote that your likelihood of success is greater than 30%, STOP! Ask yourself why you believe your chances are better than the rest of the industry. Don't continue unless you have determined that your potential is similar to that of other companies.

AVOID "QUALITY BY CRISIS" … HAVE A PLAN

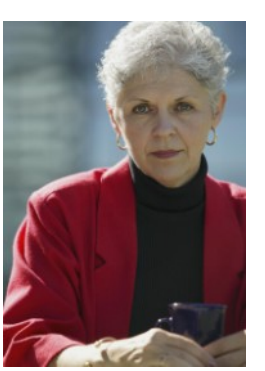
You are wise to have estimated your risk of being successful at about the same percentage as the rest of your competitors if you keep doing the same things you've been doing.

> *Patent expirations have cost life sciences companies $14 billion in revenue in 2006; an estimated $12 billion in 2007. Once generics or other knockoffs hit the market, sales typically decline 80%.*
>
> -CNN Money[11]

No one likes to dwell on the possibility of needing to improve; of competitors running past them in the final sprint to marketplace approval; of changes that might increase risks or reduce compliance; of generics breaking a 20-year patent in 11.5 years. [12] Perhaps that's why, in the past, so many companies didn't worry about time to market speed but kept their heads down and focused on just getting to the marketplace. If you don't want your company to be left behind when you're trying to do the right thing, consider the following questions.

If you need to speed your time to market:

- Where will you get your expertise?
- Who will decide where and when to start?
- How will you pay for this increase in speed?
- What will the risks be to regulatory compliance?



Today, many firms are aware that investor patience eventually wears out and that the Big Six pharmaceutical companies will only come knocking when it's in their interest to do so. When you've come up with the innovation but have burned through your funding and resources, you no longer have the ability to finish what you started and bring your new innovation to the market.

One conclusion might be that if faster time to market is needed, it will have to come at the price of either compliance, safety or efficacy. And certainly the news is full of companies and executives who felt the pressure and made poor choices, short-changing regulatory compliance or turning a blind eye to the impact on patients and people.

So, if regulatory compliance, patient safety and positive health efficacy are important and need to be priorities along with faster time to market and easier regulatory approval, what is the solution?

IS QUALITY BY DESIGN THE SOLUTION?

Does quality by design (QbD) make sense to you:

- If QbD reduces risk and improves safety and efficacy?

  ☐ Yes ☐ No

- If QbD gets you to market faster?

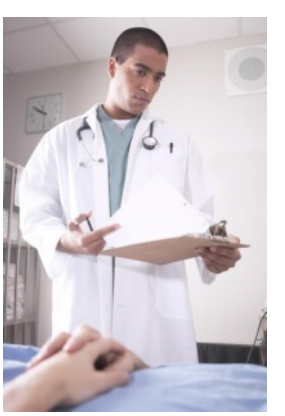
  ☐ Yes ☐ No

- If QbD is affordable?

  ☐ Yes ☐ No

Among my clients and colleagues, I have found that executives who implement quality by design generally do so because of one of the following reasons. Circle your main reason for wanting to implement quality by design.

- I do not want my work to be the cause of financial or legal liability burdens on my family, my colleagues or my company.
- I want to control costs of development and compliance.
- I want to put our treatment in the hands of patients as soon as possible.
- I want to plan ahead for market approval and get processes and supporting safety and efficacy data in place.
- I want to lower our costs of product development and compliance.



WHAT IS LEAN QUALITY BY DESIGN?

Quality by design is an affordable approach to speeding time to market and easing regulatory burdens if you can implement it without decreasing your discovery success rate or depleting your development funding.

Would you agree with this statement?

☐ Yes ☐ No

Which of these four major new product risks have you addressed?

Intellectual property	Protected?	☐ Yes	☐ No
Personnel and equipment	In place?	☐ Yes	☐ No
Regulatory compliance and approval strategy	Identified?	☐ Yes	☐ No
Time to market	Faster?	☐ Yes	☐ No

What risk, other than the cost of implementing quality by design and getting faster time to market, can you think of that would cause you to use your product development funding faster than expected?

If you are like most executives, speeding time to market may be the only initiative left with no plan. If so, quality by design is likely the last major hurdle you will have to fund.

WHERE SHOULD THE MONEY COME FROM TO PLAN AND IMPLEMENT QUALITY BY DESIGN?

If your firm is still in the preclinical stage and under 100 employees, you may be able to pay for quality by design out of today's budgetary categories. If you are in clinical trials and already depleting your funding to wrap up the final stages of market approval, quality by design is not for you. However, most of the executives I talk to have set aside some emergency money, often called "budget buffer" or "contingency money." Some of this money may be earmarked for research studies or just-in-case one-off testing to resolve unforeseen problems or isolate risks.

By now you may have concluded that without balancing quality and speed, you could severely deplete your resources and increase your risks.

If this is true, wouldn't it be fair to say that your "emergency money" or "budget buffer" is really your "quality by design fund"?

Ask Yourself These Questions…

If you remained as is today and tomorrow noticed a new competitor racing toward market approval, how long would your contingency funding last before it was depleted? How much faster would it allow you to get onto the market?

Eleven Reasons to Implement Quality by Design

Planning for faster time to market is an easy thing to put off. But if you suffer a major setback that leaves your company at risk or otherwise dependent on someone else for your success, you'll be glad you took the steps you did.

WITH QbD		WITHOUT QbD
1. You may have an expert advisor to help you plan for strong safety and efficacy in preclinical.	➡	You and your colleagues will be reliant upon expensive clinical trials to prove safety & efficacy.
2. You and your colleagues are part of a quality by design plan, but don't need to be solely accountable.	➡	You will need to risk the new product process yourself.
3. You will be able to reap faster time to market without having to pay for clinical trials first.	➡	You will need to start clinical trials first and then try to figure out how to get through faster.
4. Your colleagues and employees can be more creative.	➡	Employees may need strict supervision to stay on task. They may come to resent you.
5. You'll be able to lower your development costs by relaying on a broad knowledge base.	➡	You may have no other choice but to expend funds to fill in your knowledge gaps.
6. With more time and more funds, you may be able to choose decisions that lead to higher success rates.	➡	You may have to make risky choices based on your ability to afford results.
7. You may be able to afford to stay in clinical trials as long as you want.	➡	You may have to scale down your clinical trials.
8. You may be able to hand out bonuses you've thought about.	➡	You may have to use up your funds much faster or lose good people.
9. You may be able to make development alliances without depending on partners to succeed.	➡	Because your partners have other goals, they may not be able to provide for your success.
10. You can feel good knowing that you and your colleagues are focused on the things that matter.	➡	The cost of non-value added activities is significant factor in product development failure.
11. There may be less friction between colleagues.	➡	Colleagues may start to resent one or the other; morale slips.

FACT: According to the Food and Drug Administration, by the year 2010, the cost to bring a new drug, biologic or medical device to market will climb to $ 2 billion.[13]

What if you needed to reach the marketplace 3 years or less from now? How many years could you shave off your time to market?
_____ *years*

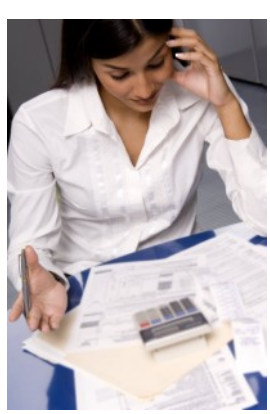
How much would that cost you? _____

FACT: Today's cost for bringing a new medical product — drug, device or biologic — through development to the marketplace reflects a 54% increase over 2000.[14]

As we get closer to clinical trials, continuing to invest in our product's development and refinement should become less important and shepherding our product toward marketplace approval more important. *Instead of investing all your R&D funds on product development, would it make more sense to use some of this to pay for increasing time to market and chance of regulatory approval instead of risking a delay to your marketplace entry?* ☐ Yes ☐ No

WHAT IS AN APPROPRIATE COST?

Startups and young firms should be able to pay for quality by design planning and implementation out of their available funding now, but as a plan B, they should be able to pay costs out of the dividends from faster time to market approval and lower development costs.



One rule of thumb I suggest my clients adopt is the "5-to-1" return on investment: the total cost to plan and implement quality by design should not exceed a 5-to-1 ratio of the total amount of marketplace speed you will gain and development costs you will save. You could, if you thought it was easier and worth it, use all of your discretionary funding you to implement quality by design using outside resources. Of course, you would only want to do this if your objectives did not consider knowledge transfer and your ability to modify and expand the program over time.

If you have only one new product and do not have a large pipeline or portfolio, how much are you able to spend after paying your operating costs? $_____ This is your maximum affordable cost to plan and implement quality by design to reach the market faster. Do not allow any external help to exceed this amount.

OKAY, QUALITY BY DESIGN IN PRECLINICAL MAKES SENSE. NOW WHAT?

After you have determined where the money come from to plan and implement quality by design, you must decide from whom you will purchase expertise or if you will try it yourself. If you decide to bring in external expertise to help you, then recognize that there are not many experts in the field. In fact, most consultants represent their companies and offer generic approaches with further add-on services. They derive very little of their income from preclinical

and product design and development compliance activities and may not be adequately prepared to help executives and business owners choose the most appropriate quality by design strategy.

Likewise, regulatory compliance professionals and consultants are generally more interested in minimizing risk as much as your money makes possible. I believe your best help will probably come from a fully independent advisor with specialties in R&D, product development and compliance. If you have a tendency to be skeptical or need to conduct due diligence, then get the answers to the questions in the next section. If the questions are answered satisfactorily, they can help you make an informed decision.

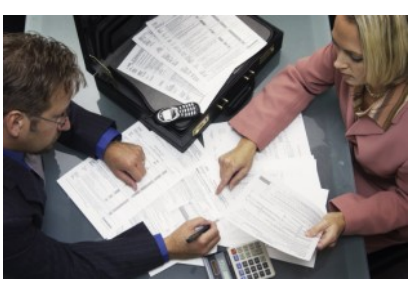
I recommend four considerations when purchasing quality by design advice:

1. **The Company.** If the company you choose to do business with has very little to no experience in R&D, preclinical and product development, you will be the one to suffer. You must feel comfortable that the company you choose has a vested interest in your success.

2. **The Proposal.** Proposals vary tremendously. You may think you're comparing apples to apples but you probably aren't. Scrutinize the proposal to be sure it allows you flexibility, minimizes your risk and give you the value and benefits you expect.

3. **The Plan.** Different consultants offer different plans. It will be up to you to determine if the plans make sense. Does the strategy take into account the evolution of your company and product line over the next five years or will you be stuck with paying higher costs as you grow or your portfolio changes? Will you have to buy more consulting to keep up with growth? Will the plan pay the dividends on faster time to market that you expect before you get to market, or will that return on your investment be redirected toward further consulting?

4. **The Price.** The price you pay is a function of how carefully you have laid out your expected value (*i.e.*, "3 years faster time to market saves us $1 million"), what your return on investment objectives are and your willingness to work out a win-win agreement with an outside expert. Most investors in your business expect a five or ten-to-one return on investment. You would be smart to use that benchmark as well.



"*You cannot afford to wait for perfect conditions. Goal setting is often a matter of balancing timing against available resources. Opportunities are easily lost while waiting for perfect conditions.*"

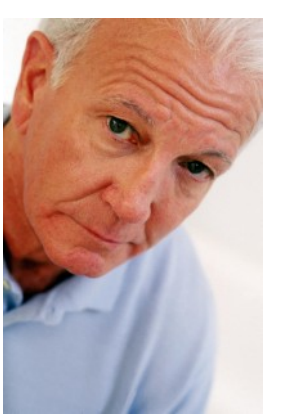
- Gary Ryan Blair, 2000

CHOOSING OUTSIDE EXPERTISE TO HELP

You should know the answers to these questions before you make a final decision about bringing in a consultant or outside advisor to help you plan and implement quality by design.

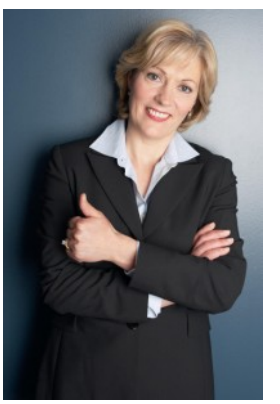
THE COMPANY

- What is the size of their average client firm? Is that a good fit with your size?
- How long has the principal worked with R&D, product development, laboratories and compliance? Does it matter? Why?
- Will you be working with the principal or a junior team?
- Do you agree with the views and strategies espoused in the firm's published articles, speeches or interviews?
- How many complaints have been made on the company in your state and in any published compliant formats (such as the Better Business Bureau)?
- Is a significant part of the company dedicated to offering quality by design and preclinical compliance advice? Is that good or bad?
- Does the firm have strict limits on the number of clients it takes on or will the firm sign deals with as many companies as it can? How could this affect you?



THE PROPOSAL

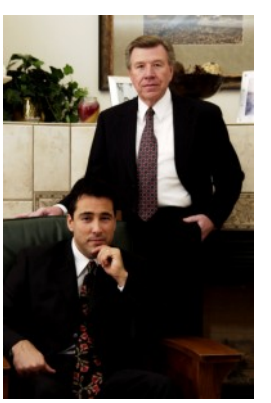
Proposals tend to differ in the ways listed below:



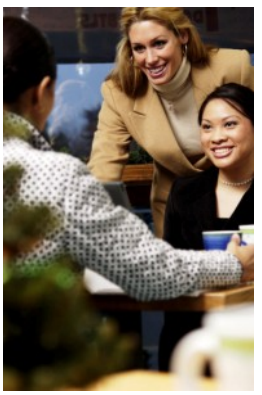
- Did the firm give you a chance to review their assessment of the situation before giving you a proposal?
- How many times did the firm talk with you to clarify specifics before providing a proposal?
- Does the proposal provide clear expectations of objectives? Did you get a chance to review and revise them based on your understanding? If not, what might this indicate?
- Does the proposal provide phases or mini-projects to give you early results and reduced risk? Can you walk away after each phase with no further commitment or penalty?
- Does the proposal provide options for levels of engagement or is it dedicated staff augmentation? Note that the inclusion of resumes in a proposal is often a dead giveaway to the latter.
- Does the proposal draw a clear distinction between costs included and excluded (*i.e.*, travel, materials, subcontractors, administrative support, etc.)?
- Does the proposal recognize and refer to any non-disclosure or confidentiality terms and conditions?

- Does the proposal provide a written guarantee? Are there third -party standards of ethics referenced? Can you collect more than your investment if the work is utterly unsatisfactory?
- Does the proposal disclose an available payment discount (for instance, 5% upon payment in full, discounts for referrals, etc.)?
- How often will you have regularly scheduled check-ins for both progress and to improve your working relationship and return on investment? Is this important to you?
- What post-project support will you have from the consultant? Will you receive help preparing for an audit after the project's over?

THE PLAN



- How much do you expect your company to change over the next five years? What are the trigger points in the plan to adjust strategy and tactics?
- Will you need to bring in another consultant later to account for changes or is knowledge transfer built into the plan?
- What guarantee do you have that the consultant isn't looking to supplement staff long-term?



- What is the average length of time your colleagues and competitors have hired a consultant for? Is this plan different? Why?
- Based on the average, how long will it take you to reach marketplace approval? Does the plan highlight realistic areas to target for improvement?

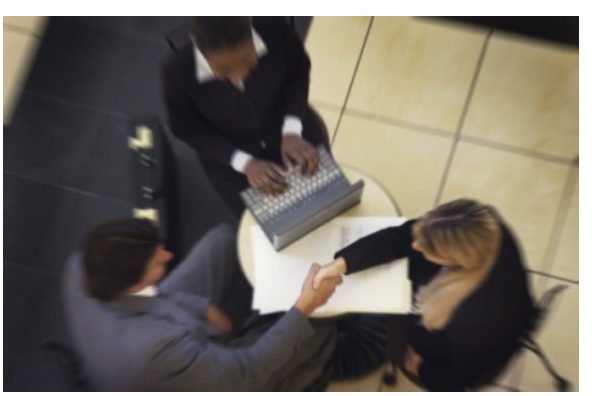
THE PRICE

- Can you pay the consultant without affecting your growth plans or depleting your resources even if the project was delayed by as much as 20% at some point in the future?
- Does the investment required match the long-term value of the engagement? (Generally, the more value, the higher the cost.)
- Can you expect at least a 5-to-1 rate of return?
- Has there ever been a situation where the consulting firm has had to raise fees on existing clients in mid-project?
- Does the company charge an initial, non-refundable fee?
- Is there a qualified referral discount or payment in full discount?
- Is the firm able to offer high service and quality in exchange for less on-site and travel costs?

- Does the company focus its senior people on its clients at hand or only on the ones who bring in more than $450,000? How could this affect you?

Be very careful if the costs you are considering are dramatically different from the prices of another company for a similar proposal. Smaller, boutique firms tend to have less overhead which translates into lower fees than larger firms. However, keep an eye out for companies that offer a steeply lower fee; they may intend to raise their rates later on to make up for a low rate to get your business.

It's better to know the answers to these questions now than to wait until midway through the project or the proposal phase. Unfortunately, many consulting companies sell with their seniors and then perform a bait-and-switch, servicing their non-million dollar accounts with junior consultants. You need to feel comfortable knowing that your company is a top focus of the consulting firm.



The answers to most of these questions can be answered by an experienced consultant. Call the independent expert who gave you this book.

This booklet, prepared for executives searching for a solution to faster time to market and wondering about the FDA's quality by design, is designed to provide you reliable, verifiable facts, figures and insights so you can make an informed decision about the feasibility and affordability of quality by design for faster, better, easier product development for you and your organization.

John Avellanet, the author of *Is Quality by Design Right for My Organization…?*, is internationally known for his expertise in regulated R&D and product development, and offers specialized advice in cost-effective compliance, intellectual property security, and IT compliance. Prior to starting his consulting practice, John was the CIO of a *Fortune 50* medical device subsidiary and was accountable for compliance with the FDA's 21 CFR Part 11 plus ISO-17799 and ISO-15489. He is available as a speaker and facilitator for on-site seminars.

For reprints of John's other publications, see the resource library of his company, Cerulean Associates LLC, at: *www.ceruleanllc.com*

BONUS

FIVE STARTING STEPS TO QUALITY BY DESIGN

To help you start planning and implementing quality by design in your organization, here are five straightforward steps you can take today.

1. **Run Lean.** Assess your new product pipeline. How many ideas, innovations, new products are you trying to develop? Trying to run too many at once is a recipe for errors and delays. What are your processes in place to deal with new ideas and innovations that crop up throughout the development process?

2. **Slack Time.** Just as you build in a budget buffer, you must also have down time for people. If you schedule your employees and teams at near capacity, any single misstep, delay, sick day, etc., will start a chain reaction of delay. If you build in a 15% financial buffer over-run, make sure that in a 40 hour work week, you have a good 6 hours wherein your colleagues are not scheduled for running tests, writing reports, attending meetings, and so on. Remember the successful project manager's mantra: *A month has 20 workdays, not thirty*.

3. **Reduce Queue Time.** Avoid stress overloads, poor morale and corner-cutting by reducing queue times for testing, drawing, prototyping, assembling, etc. to no more than one or two weeks. Use outsourced contract labor or laboratories as your safety valve. Draw process maps and identify typical bottlenecks or non-value added steps.

4. **Use Universities Wisely.** Rather than avoiding non-good laboratory practice-certified university labs, embrace academia to reduce your workload and gain product characterization insights. Ask university laboratories to test and verify non-critical product components, discount variants, engineer out variability, or conduct feasibility modeling with computer simulation systems (such as SimuGen).

5. **Build on Existing Knowledge.** Rather than reinventing aspects of a project, or retesting earlier results, look for ways to use existing information to speed your product design and development. Literature surveys of toxicology reports, publicly disclosed failed clinical trials or adverse affects, university publications or professors active in the industry can all be sources of viable information to help you shape your decisions. What can you learn from early discovery testing? Did you "bookshelf" your previous new product development work so as to draw upon it later to support current development efforts?

A lean quality by design program in the preclinical stage is crucial for speeding time to market and easing regulatory approval. For any decision that arises, ask, Is this really a necessary step for us to take? Does it provide proof of our product's safety and efficacy?

Your company may be one of many expending a lot of effort testing new product attributes that are important to safety and efficacy … and those that are *not*. If you need more advice on successfully implementing quality by design, contact a fully independent expert. The questions in section two will help you make a good decision.

- J. Avellanet

ENDNOTES

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