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DOES YOUR CRO REALLY KNOW THE FDA?

This probably isn't news to you: The FDA has mountains of regulations and almost no one knows all of them.

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ABOUT PRINCETON PHARMATECH

We provide clinical trial biostatistics and programming solutions to the pharmaceutical, biotechnology, life science and research industry.

Does Your CRO Really Know the FDA?

This probably isn't news to you: The FDA has mountains of regulations and almost no one knows all of them. So, with such a wide information gap, it's critical to work with CROs that have a deep understanding of FDA regulations. Any mishaps or misunderstandings will cost your organization tens of millions of dollars in additional development time. That doesn't even include what you're going to lose when it comes to delaying your time to market.

Just How Powerful Is the FDA?

A paper from Wharton's Public Policy Initiative notes that the FDA has the power to "fundamentally alter market outcomes." This is an extremely polite way of saying that your drug, device or treatment might be the best one in the world, but if someone else's similar product passes the FDA first, they're going to get the credit — and the profits.

The FDA holds jurisdiction over $2.4 trillion of the economic activity or approximately 25 percent of the nation's economy. Employing over 14,000 people with an annual budget of $5.1 billion. The largest numbers of FDA employees work in Regulatory Affairs, the Center for Drug Evaluation and Research, the Center for Devices and Radiological Health and the Center for Biologics Evaluation and Research. The FDA enforces over 200 laws dating back to 1906, each with their own use cases and application history.

Medical device and drug manufacturers know that the FDA is the most important regulatory body in the country. But it's also one of the most powerful regulatory agencies in the world.

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Are We In a Period of Decreased FDA Oversight?

A comprehensive meta-study from JAMA

A comprehensive meta-study from JAMA sheds light on just how real the problem of not knowing the most up-to-date FDA regulations can be for your organization. Fifty percent of all new drugs were rejected upon first submission. Only half of the ones that failed were ultimately approved. A mere 13 percent of these rejections were at all related to efficacy.

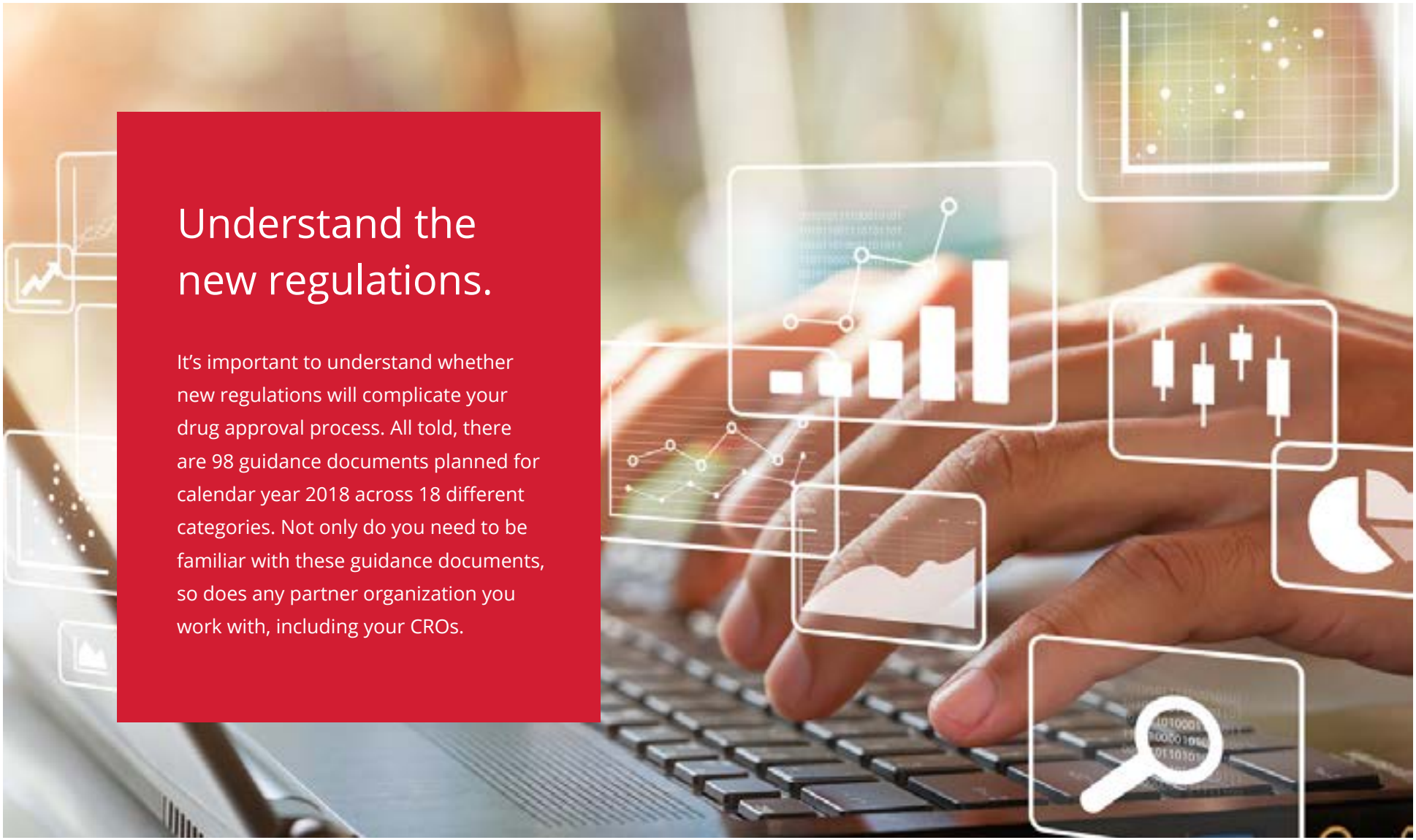
98 guidance documents planned for calendar year 2018 across 18 different categories

Don't believe the hype about supposedly lax regulations under the new administration. While PwC reported a decrease in what it called "significant" regulations under President Trump's FDA, the weasel word here is "significant." The oft-cited report itself states in no uncertain terms "the FDA has not slowed its creation of policy." This also refers only to the first year of the Trump Administration. The previous Republican administration, under George W. Bush, oversaw a whopping 100 percent increase in the total number of regulations during its second year alone.

The "decreased oversight" of the Trump Administration refers to what PwC calls "economically significant" regulations, not the number of regulations. Whether or not a regulation is economically significant is of little interest to your organization. It's more important to understand whether new regulations will complicate your drug approval process. All told, there are 98 guidance documents planned for calendar year 2018 across 18 different categories. Not only do you need to be familiar with these guidance documents, so does any partner organization you work with, including your CROs.

Indeed, Deloitte refers to "regulatory uncertainty" for 2018 and beyond. Its report cites the booming field of medical device development as a particularly troublesome area as the FDA seeks to enact regulations up to the challenge of securing 21st Century devices. The same report notes that the implications of the 21st Century Cures Act are still shaking out, one pillar of which is the modernization of clinical trials. This might ultimately result in fewer regulations. However, it still hints at an ever-changing landscape of FDA regulation.

Regardless of whether you view these regulations as the functional equivalent of a safety belt or an expensive intrusion is largely besides the point. What is far more relevant is that they exist, and working with a CRO unschooled in emerging FDA regulations can cost your organization its approval. As explored in our recent white paper on CRO accuracy, the cost of a delayed approval is one million dollars per day for an average of three months.



Understand the new regulations.

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The Emerging Regulatory Landscape

Often, new FDA regulations can be difficult to understand, especially before they have extensive case histories to extrapolate meaning from. A great example of this are the new compounding pharmacy regulations for 2018. New regulations have been put in place to encourage the registration of compounding pharmacies. Some of these exist to protect intellectual property, while others are designed to improve safety. This will place additional restrictions on these facilities, sending ripples throughout the industry.

In other cases, the bar moves lower, but you still need to know where the target lies. For example, there has not been a new Alzheimer's drug approved in more than ten years. New regulations focus specifically on long-term cognition rather than demanding that any Alzheimer's treatment keep a patient more independent for longer. That broadens the playing field, but your organization will still have to meet specific metrics for the first Alzheimer's approval in over ten years. What are those metrics? It can be difficult to tell before someone fails approval.

The problem of new regulations is particularly acute among those in disruptive, innovative or on-the-edge medical technologies, such as stem cell research. New stem cell regulations are set to go into effect in 2021, which might seem far away to most but is right around the corner in terms of development cycles. You and your partner data analysis CROs need to prepare for these coming realities right now.

Further new regulations loom on the horizon. The FDA has long sought to change the intended use regulations. While these have currently been delayed pending comment, they won't be too far away. That will be yet another minefield your organization will have to navigate to ensure compliance.

This doesn't even bring into account "guidance," which is supposed to be non-binding — but virtually every pharmaceutical organization knows better.

Where Regulatory Missteps Occur

When it comes to submitting your new drug to the FDA, new regulations might not even be the issue. You might just bump up against existing regulations you think you know. However, the terrain of an FDA approval is an uncertain and changing landscape with many gray areas. Common problems crop up even with large and experience pharmaceutical organizations who have extensive legal teams and in-house research departments. Common issues include:

EFFICACY

Since passage of the Kefauver Harris Amendment, you must not only prove to the FDA that your drug is safe. You must also prove that it is efficacious. Indeed, the entire third phase of testing revolves around proof of efficacy. This is a much higher bar. Prior to the passage of this Amendment, the average passage time was a mere seven months as opposed to the several years that's the norm today. Small data inaccuracies or a failure to properly document your work means you're going to be sent back to the drawing board to prove the efficacy of your new drug.

DOCUMENTATION

Remember that the FDA doesn't just want your results. Just like in middle school math class, they want you to show your work. Failure to do so—in excruciating detail—can throw you into non-compliance and result in your organization frantically backtracking to find where it omitted key data. The smallest error in your work or the documentation thereof means you're spending a million dollars a day while your competitors soldier on.

PATIENT POPULATION

The FDA is generally not a fan of small, poorly defined patient populations. What's the optimum number of patients at any given point in time? How should these populations be defined? Even if you're working with a CRO that isn't conducting your patient trials, it should be familiar with best practices and current trends in the FDA to evaluate your existing data efficiently and effectively. The right CRO will have no problem looking at your data and determining that the patient trials aren't going to pass muster.

VALIDATION

This relates to documentation, but isn't quite the same as "checking the work." In this case, the FDA evaluates the drug's target, class and mechanism of action. The right CRO will be able to tell you whether you're checking the right boxes for each. Note that this is where the rubber hits the road a lot of the time with regard to FDA approvals and regulations. A CRO familiar with current FDA practices regarding what niche your drug will go in can help to tailor your data and reports in the most pleasing method possible for the FDA.

TRIAL COMPLEXITY

In some cases, the FDA has higher regulatory burdens. In others, your patient pool might be too large, requiring additional studies to drill down into demographics to get a better sense of dosage and if the drug is even effective and safe for everyone. The right CRO emphasizing data analysis can look at your extant data and tell you if the FDA is likely to require additional data before approval.

MISCLASSIFICATION

With $1.3 billion lost in Medicare rebates due to misclassified drugs, misclassification is certainly a big issue when it comes to getting your drug approved. Not only do you want to classify your drug correctly to get it approved, you want to get it classified correctly so that you're in compliance with regulations once it goes to market, including but not limited to any rebate programs.

These are just some of the most common regulatory snares you can fall into with existing regulations, to say nothing of emerging ones. Indeed, the world of FDA regulations is one fraught with constant controversy and debate with regard to what the right level of oversight is. The FDA, at least in theory, always seeks to strike a balance between patient protection and ensuring efficacious new treatments reach the market to reduce suffering.

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Current Controversies in the World of FDA Regulations

Most medical organizations know that FDA regulations are always a game of political football, with an ever-moving set of goal posts. New administrations (and administrators) come in and must deal with both what is and what their intentions are. Some currently emerging issues in the world of FDA regulations include:

INTERNATIONAL COLLABORATION

With the FDA regulating products made in more than 150 countries, the pharmaceutical and medical device worlds are now global ones. However, collaborating across borders is catching up in terms of regulatory oversight. If any of your research is conducted overseas you must partner with an organization who knows how this should be presented to the FDA to pass muster.

OFF-LABEL USE

The FDA is well aware that nearly every drug is used for something other than its intended effect. They're aware doctors prescribe drugs for effects that are nominally side effects. Some off-label use is currently in flux as the FDA recently lost a case regarding its regulation of off-label use.

GENERICS

First generics are a hot-button issue with the FDA at this time. Although the FDA is, in theory, always trying to find ways to speed up the approval of generics in general and first generics in particular, the practice has lagged behind. Specifically, labelling remains a contentious issue.

PATIENT ADVOCACY

Patients, particularly those with terminal conditions, are always looking for faster drug approvals to relieve their symptoms. The FDA is looking for ways to improve time to market for drug manufacturers without sacrificing consumer protection factors.

LAB-DEVELOPED TESTS REGULATION

Lab-developed tests (LDT regulation) is similar to the conversation around generics. The FDA wants to ensure safety for consumers while also searching for ways to get new, effective drugs to the market sooner. This area is in great flux at the moment and if your organization leverages LDTs for research, it is absolutely crucial to have your data assembled by a CRO familiar with the FDA's most current thinking on the matter.

These are just a few of the current controversies within the FDA which can impact the approval of your drug. It's important to work with a CRO abreast of the current debates internal to the FDA. This can help your organization to remain ahead of the curve in terms of its research and development.

Digital Products and FDA Approval

The uncertain landscape of FDA regulations is felt nowhere more sharply than in the digital sphere. Here you need to conform not only with safety and efficacy standards, but also best security practices in an ever-changing landscape. The FDA breaks digital products down into three different classes.

CLASS I

This class of devices and digital products has such a low risk that there's virtually no regulation associated with it. You'll still have to be in compliance with FDA standards, but you won't require approval to bring a Class I device to market.

CLASS II

Now things start getting a little riskier. This class of products requires 510(k) approval. However, the bar for clearance is lower than the next class of products.

CLASS III

Class III is the most dangerous but also the most life-saving class of products. These devices are generally implanted in the body or are completely new, so the risks associated with them are not well known or understood.

Both Class II and Class III require FDA approval. This is the right razor edge of regulation, with a regulatory environment trying to keep pace with an emerging technology. To confuse matters even more, the FDA has stated that it will exercise "enforcement discretion." This muddies the waters significantly for those seeking FDA approval for devices in these classes. Will the FDA enforce the existing guidelines for your digital product or not?

What's more, there might even be ambiguity regarding whether or not your product is digital or traditional. Sound silly? It's not. Especially if your product has a digital component and a non-digital one, such as digital pills.

Working with the right CRO can help you navigate the system properly, significantly improving your chances of approval for an innovative medical device that could potentially save thousands of lives.

What Your CRO Should Be Thinking About

Your biostatistical CRO should be concerned about the approval process on your behalf. There are some guidelines used by the FDA a biostatistical CRO should be familiar with to ensure the highest possibility of approval. Checking to see if your biostatistical CRO is familiar with the following information is a great first step toward evaluating if they're the kind of organization you want to partner with:

- **ICH9:** This is specifically a guideline for the statistical analysis portion of the approval process. It's worth repeating that the FDA will closely check every line of your statistical analysis. So not only must the results be accurate, but also every step to get to those results. What's more, the information must be presented in the right way to satisfy the FDA.

- **Advisory Committee Meetings:** Today's advisories are tomorrow regulations. Your biostatistical CRO should be up to date on advisory committee meetings — what happened there and why and what it means — as well as emerging regulations. If your drug is at all similar to drugs discussed during recent Advisory Committee meetings, you will receive a treasure trove of information from your CRO about what the FDA is looking for as pertains to your treatment.

- **Non-Binding Deadlines and Guidelines:** While some rulings might be "non-binding" that doesn't mean your partner CRO shouldn't be familiar with them. Such familiarity with even "non-binding" deadlines and regulations can only help to bolster your case when you present your data to the FDA.

Addenda: Often times, a new regulation or finding isn't the end of the matter. Relevant material can also be obtained from addenda added to findings months after the fact. The FDA isn't always great about communicating this information in a timely manner, so having a biostatistical CRO who can alert you of it where necessary can be a huge value add.

Methodologies: The FDA can also object to your methodologies, regardless of your data, its accuracy and your documentation thereof. The right biostatistical CRO partner knows what methodologies the FDA prefers at any given time and can steer your research in that direction. The best result here is that not only do you get your drug approved, but your methodology becomes the gold standard for the industry.

Committee Practice: Difference committees at different stages are... well, different. Some are at the vanguard of a standard, others lag behind. Some have broader ideas of what regulations mean, while others are very strict, by the book and literal. Different committees at different stages use different formats for reports. Your CRO should know how to best present your material to the relevant committee you're going to be presenting to. Because not all committees are created equally.

Design Protocols: A general CRO might not design the best study. A biostatistical CRO specializing in data analysis can let you know where this study might fall afoul of the FDA. You can then find where to make changes to your study — how much of your study and data can be kept, what needs to be massaged and what just isn't going to cut it.

The above list is not exhaustive regarding how you can assure your biostatistical CRO is up to speed on how to help you navigate the process. It is, however, a good checklist as a starting point to begin evaluating who you will work with.

Auditing Your CRO

An audit of your CRO can help provide an overview of how familiar they are with the newest and most current FDA regulation. Sponsors should perform an audit at the beginning of the relationship as well as ongoing audits throughout the process. This will provide you with a thorough picture of your CRO and its areas of expertise, including their attention toward the shifting landscape of FDA regulations.

If you're coming into a position working with a legacy CRO, this should be a part of your due diligence when reviewing existing relationships. In fact, you might be surprised to discover no audit has been done with your existing CRO relationships. This isn't necessarily a red flag. A failure to properly audit could just be par for the course. However, it is a signal that your organization needs to conduct a thorough audit of your present CROs — and probably some other partner organizations.

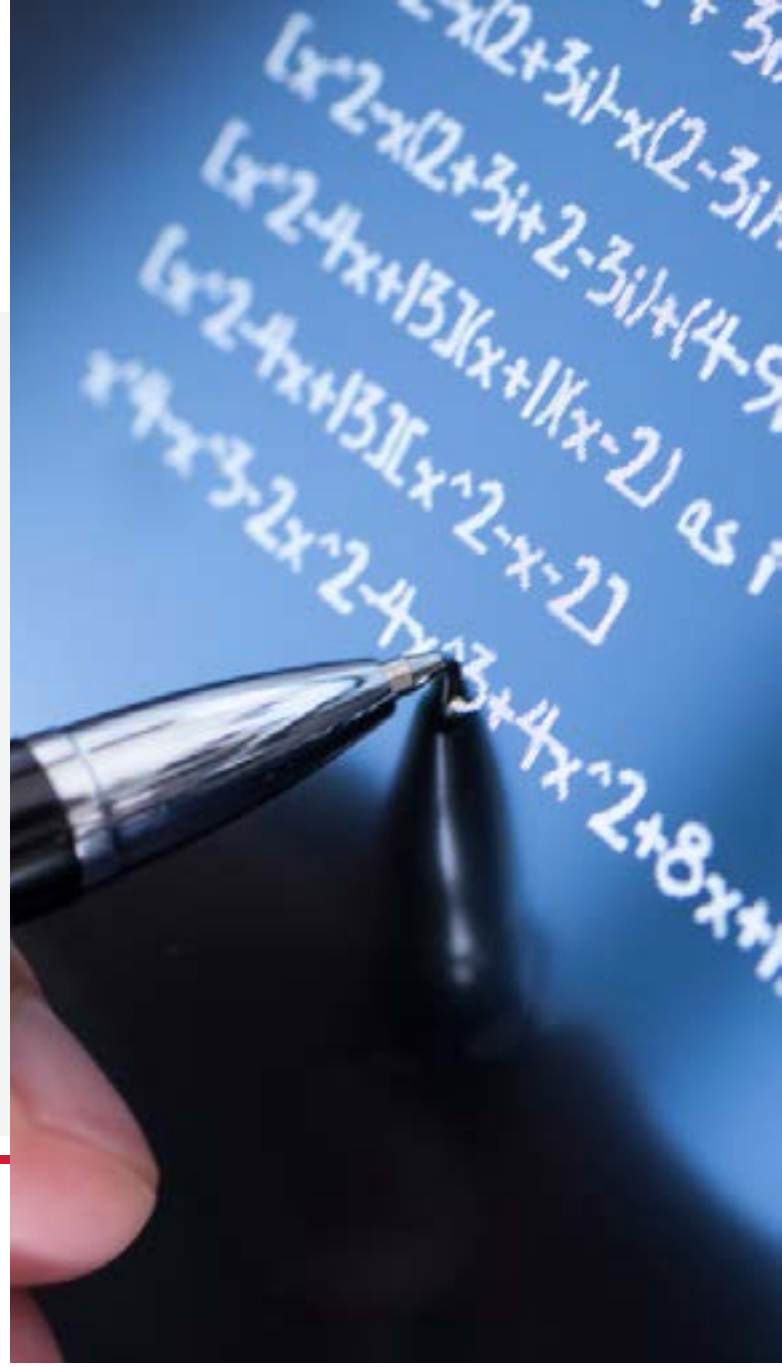
Do you have to hire an independent organization to conduct your CRO audit? Maybe, but it's not necessary in every case. Conducting your own audit can be logistically complicated, but you probably already have all the tools necessary to do it. Whether or not you can herd the cats of QA, data management, safety and clinical operations together to conduct a thorough audit is another question, but these tools are already in your toolbox.

When it comes time to audit, what are you actually looking for? Some key areas to pay extra attention to include:

- **Experience:** Experience is one of the main things to look for. This doesn't just mean what the company does and has done, but also what they do in the here and now to keep up with a quickly changing field. Knowledge of FDA regulations is certainly a part of that. It might be difficult to quiz a partner CRO on the most current FDA regulations (especially when your organization's knowledge might be somewhat lacking), a company culture of education and professional development speaks well to an organization's knowledge of breaking developments in FDA regulations.

- **Stability:** Stability is a major factor in how well-oiled your partner CRO's machine is. A high turnover rate often speaks to poor hiring practices not limited to an inability to mesh with company culture, understand SOPs or effectively perform job duties. An organization which maintains the same staff year over year is an organization can mean you're working with an organization more than the sum of its parts.

- **Training:** You're not necessarily looking for organizations whose team have taken classes specifically in FDA regulations — though that sure wouldn't hurt. More likely, however, is the company culture of training, education and development outlined above. Frequent training hints at a greater working knowledge of FDA regulations as they emerge. That bodes well for your organization.



When in doubt, don't be afraid to schedule in-person interviews with a CRO's team. This isn't the norm for auditing, but it's not out of the ordinary. The right organization will happily allow their people to sit down with yours to discuss their working knowledge of emerging FDA regulations.

When It All Goes Wrong: Late Stage Clinical Data Analysis

Here's a problem that goes beyond simple headaches into downright nightmare. You get to your late-stage clinical data analysis and you find that some regulation has been forgotten or even that your data is inaccurate. The latter is discussed in our last white paper. The former, however, is just as pressing of an issue, especially when your primary consideration when choosing a CRO is based on price.

PHASE THREE IS THE HARDEST STAGE OF THE APPROVAL PROCESS

Phase three is the most rigid of the approval phases by far. Studies can change during phases one and two. Sometimes the studies run during the earlier phases are far less rigid than those required to pass muster during phase three. But once the wheels of the FDA approval process start rolling, there's no way to stop them. Your lack of preparedness is not the FDA's problem — it's yours. So you have to make sure everything aligns properly as you move into phase three. Not only do your studies need to be bigger, they also need to be more precise and will be subjected to far more scrutiny.

Where Regulatory Missteps Occur

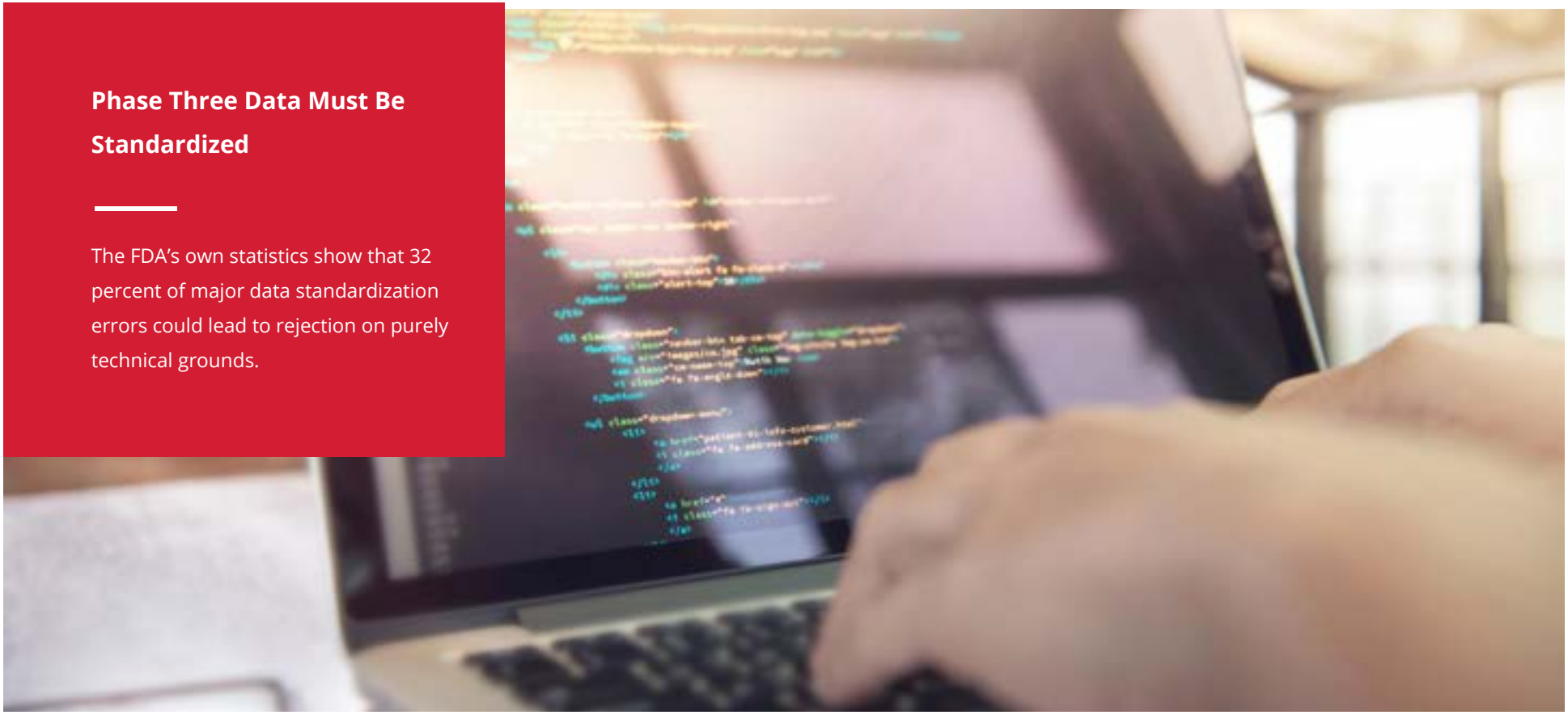
1. Efficacy
2. Documentation
3. Patient Population
4. Validation
5. Trial Complexity
6. Misclassification

THE FDA WILL MERCILESSLY CHALLENGE YOUR ANALYSIS

Your analysis will also be challenged, underscoring the need to work with the right CRO. The right CRO is not only highly precise with its data analysis, but also knows the FDA inside and out. This allows them to anticipate any phase three objections the FDA might have to your data. You might not want to hear what's wrong with the data you have, but it's going to be a lot better coming from a partner CRO than it will be coming from the FDA.

Phase Three Data Must Be Standardized

The FDA's own statistics show that 32 percent of major data standardization errors could lead to rejection on purely technical grounds.



YOUR OLD RESEARCH MUST ACCOUNT FOR NEW RESEARCH

In addition to anticipating objections your partner CRO should be familiar with the field you're in and the latest research. Many times, the FDA will come back not saying that you're data is shoddy or your analysis is imprecise, but that you're simply behind the curve and that new research hasn't been taken into account. The right CRO will be able to tell you this before the FDA and also be able to provide you with the latest research in the field, allowing you to tailor your study to the new realities of your field.

Phase Three Data Must Be Standardized

Your data must be standardized for phase three. This means taking all the data from all of the studies and fitting it to the appropriate FDA guidelines.

Your data must be standardized for phase three. This means taking all the data from all of the studies and fitting it to the appropriate FDA guidelines. Even small errors with regard to standardization can have you going back to the drawing board.In fact, the FDA's own statistics show that 32 percent of major data standardization errors could lead to rejection on purely technical grounds. You won't be starting from scratch as such, but you will be losing an average of $1 million per day every day that your approval is delayed. This doesn't even take into account the intangible costs like a loss of investor confidence in your project or negative industry buzz associated with the delay.

Emerging issues in the world of FDA regulations

1. International Collaboration
2. Off-Label Use
3. Generics
4. Patient Advocacy
5. Lab-Developed Test Regulation

YOUR BIOSTATISTICAL PROGRAMMING MATTERS

Every data set from every study ever done must all be brought together for approval. What's more, the collated and synthesized data has to have the same integrity as each of its constituent parts. This facilities easy comparison across each phase of drug development and testing. Biostatistics CROs specializing in data analysis have software and methodologies specifically designed to harmonize your data across studies. This simply can't be done in an efficient and elegant manner without such software. Without it, each data set and protocol has to be updated individually. Often times, everything has to be done all over again once a third data set is introduced into the first and the second. Usually that's because the third pass introduces data inconsistent with the first two. Sophisticated data analysis software, on the other hand, determines the best protocol to use across all datasets before it begins to collate them all.

YOUR META-ANALYSIS ENCOMPASSES POTENTIALLY DECADES OF DATA

The final meta analysis requires extensive knowledge of each study, how they fit together, how the FDA reacted to each when it was first conducted, how the FDA is likely to react to the data inside them today and how to best present the data to the FDA when you finally submit all of your data for approval. Any new analysis must have the same results as previous analysis or else you're going to be doing more research and analysis yet again. Worst of all for your organization, the timelines on which these analyses must be performed and presented are very tight, not leaving much room for any error.

ONLY A SKILLED BIOSTATISTICAL CRO CAN HANDLE THE PHASE THREE INTEGRATED ANALYSIS

Errors or slow progress understandably create sponsor anxiety. There's simply no substitute for a CRO specializing in statistical data analysis and late-stage integrated analysis once you enter phase three. Even when your data and analysis is impeccable in the first two stages, someone must skillfully craft a seamless story for all three stages. And when your data is not impeccable, you need someone who can identify precisely where other partners went wrong and how to fix it.

Data errors and inconsistencies must be caught before you present to the FDA. There's simply no other option. To not do this is to ask for millions of dollars in fees and significantly delayed time to market. Only the right biostatistical CRO, skilled in data analysis and integrated data analysis can protect you from the possibility of rejection. That means rethinking how you choose CROs — not searching simply for the lowest bid, which often isn't even the lowest price, but looking for the most skilled CRO with a background in your field.

We believe price shopping for a CRO is a mistake. Please review our recent white paper on accuracy. Then schedule a one-on-one briefing with a Princeton Pharmatech representative today about how we can conduct your data analysis to prevent any potential problems with the FDA.

What Your CRO Should Be Thinking About

1. ICH9
2. Advisory Committee meetings
3. Non-Binding Deadline and guidelines
4. Addenda
5. Preferred Methodologies
6. Committee Practice - Reports
7. Design Protocols

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