Q&A

A Fresh Perspective from the FDA on the Final IND Safety Reporting Rule

In a recent WCG webinar, Steven Beales, Senior Vice President, Scientific and Regulatory at WCG, facilitated a conversation with FDA leaders, Robert Temple, the Deputy Director of CDER, and Jacqueline Corrigan-Curay, the Director of the Office of Medical Policy. They discussed overreporting of SUSARs and the impact on patient safety. As part of that conversation, Temple and Corrigan-Curay answered questions posed by Beales and the audience, many of which are included here.

Please note that the questions and the responses have been edited for length and clarity.

Q: Why do the FDA, investigators and IRBs continue to receive large numbers of uninformative safety reports that do not comply with the final rule for IND safety reporting?

A: (Temple) I'm sure part of it is anxiety over not reporting something. But the main reason is that it's not so simple to do, especially for a small company with no safety experts. If you are a small company with no safety experts, you have some obligation to get a safety assessment group together. This is a fundamental requirement of a sponsor to monitor safety.

Sending a report that doesn't really look like an adverse effect of the drug is a waste of everybody's time. It wastes the time of our people too. They do have to read them. They can't just ignore them. That's not responsible of you to report.

It also flies in the face of what we're really hoping for, which is serious analysis of the events. If you just report everything, you might miss something important. That could be a disaster. If there's isn't a serious analysis, you're not really protecting the public or protecting patients the way you promised to.

Q: Is it acceptable for a site to have a policy stating it will acknowledge reports from sponsor only when those reports deal with unanticipated problems that lead to a protocol change or some other change in study conduct?

A: (Corrigan-Curay) When we receive an IND safety report, we assume the sponsor has done the analysis and is complying with our regulations as the best they can. It is often a judgement call. Under our regulatory framework, investigators are expected to review these reports to protect patient safety. If they're being reported under what our regulations require, then they are unexpected and serious. There is some evidence that they're possibly related.

They need to be provided to the IRB because, as we've stated clearly in guidance, we think they meet the criteria of an unanticipated problem.

In terms of reviewing thousands a month—we realize that is a problem for the clinical trial system and for safety. If all of these events were unexpected and possibly related, that would be a problem potentially for the drugs. There needs to be greater dialogue about why they're being reported if they're not useful. You're communicating to us that the current guidance hasn't done everything we needed it to do. And so what else can we do?

We're willing to keep engaging on this. We have seen some companies very successfully, implement different procedures that allow for aggregate analysis and really teasing out where we think there is a threshold. 'How do we bring those best practices forward in other settings?' and 'What are the barriers to doing that?' are important questions.

Q: To follow up, only the largest pharmas with the scientific expertise, large pharmacovigilance departments, etc., have been able to implement this guidance. Do you see changes in the guidance coming soon? Or do you see regulatory consequences if sponsors continue to ignore your suggestions and recommendations?

A: (Temple) I think the first thing we have to do is get a better idea of just what we're actually getting and determine how uniform it is. Maybe you're right: Maybe it is big companies vs. small companies. But we need to get more details. I don't think it's out of the question that we would write guidance on how to do this better, and what the typical errors are and why.

Again, it's important to emphasize that doing it the wrong way not only makes work for people, but it also gets in the way of learning about the things that matter. I think that's our most important and most critical argument. That's the one that I think we should be prepared to talk about. It gets in the way. You might miss something that matters because you've just thrown everything over the wall.

Sponsors have indicated that they think the FDA inspectors are sometimes more conservative and traditional on the guidance that you yourselves are. Is that a possibility?

A: (Corrigan-Curay) Well, I think certainly we try to keep our inspectors up to date on policy changes. I would also say, I believe in the past couple years, our inspectorate has actually been reorganized a bit, so that we have inspectors who focus on different areas. If you're an inspector for clinical trials, that's really where you're going to focus. If folks have examples of it, and we need to have some more internal discussions, we're always happy to have such feedback.

Q: Bob, you wrote some excellent guidance on safety assessment committees. Can you share your thoughts on their usefulness in addition to other mechanisms in place, such as DMCs?

A: (Temple) Well, we never said you have to have a separate safety assessment committee. The trouble with the DMC is it's usually directed at a single study. But as we say in our guidance, if you evolve the DMC so that it looks at multiple studies, that's perfectly okay. They just need the appropriate competency to be looking at the accumulating data. They need to be knowledgeable enough about safety and related issues, and they need to be able to do analysis. What you call it is not the most important question. But there needs to be a group that can do this, and probably one person doing it alone is not enough.

A: (Corrigan-Curay) If you're a small company, but you have a DMC, can that DMC take on this role and help? We certainly would think that's possible. The real issue is that there must be a different SOP for the DMC when they're operating in this space. They aren't

doing the risk/benefit analysis in terms of whether their trial continues. Now, they are applying our standards and asking "Is there evidence to suggest this event is related?". They would need training to make sure which question we're answering and whether they're willing to take that on.

Q: Does the FDA provide any kind of training in this regard for sponsors who are looking to compose such a committee?

A: (Temple) We've said a little bit about the expertise you need but not in a 'here's how to form a committee' way.

A: (Corrigan-Curay) When we write these guidances, we're trying to provide guidance but not limit some flexibility in implementation. We provided some examples of the types of folks who might be on a Safety Assessment Committee. But we also said, depending upon the program, it could be a larger group or a smaller group.

Q: Why is artificial intelligence, or similar technology, not being applied to the clinical trial space?

A: (Corrigan-Curay) Judgement is required. Not that AI doesn't have judgment, but it's been challenging to apply AI and machine learning to things like clinical records. Things are not always represented in the same way. AI could perhaps be used to identify patterns for additional analysis, but I don't think we can replace the clinical and other judgments, and quantitative reasoning that goes into deciding, especially in the aggregate situation, where you've reached a reporting threshold. I think we should explore tools for that, but I don't think that we can put this all on AI to solve the issue either.

There's been more exploration of AI on the post-marketing side, where the volume is even greater.

A: (Temple) Imagine those approaches being attached to a very huge trial being done under an IND: A 10,000 patient outcome study might benefit from AI.

Q: In terms of global harmonization, sponsors feel they're having to do double work. Let's say we've got patients who are bleeding severely, and we're into the aggregate analysis. We're continuing to get events, we're sending them off to Europe, Japan, etc. Sponsors lean toward sending it to the FDA, just in case. "Better to send than not send," is a prevailing view in the industry. Do you have thoughts on that?

A: (Temple) My thought is that we have specifically said, that is not what we want you to do. We do not want to hear about every serious event, especially if it's something that happens in the population even without the drug. We want them to analyze the rate of these events in the treated and the untreated group, and then send it to us as the aggregate

analysis. We quite clearly don't want them if they don't meet that test.

Now, what the threshold is for deciding that it meets the test could be debated. Do you need nominal significance or is a good strong mean enough? Those are judgment calls. But just the fact that it happened, that someone had a heart attack, that's a serious event. But that doesn't mean the drug did it and we do not want to see those reported to us.

Q: Can you compare ICH-E6 ADR phrase "reasonable possibility cannot be ruled out" with 312.32(a) "evidence to suggest a causal relationship? Are they the same standard? Given that ICH-E6 has been accepted by the FDA as official guidance, are we in effect asking sponsors to follow two separate standards?

A: (Temple) I think those two phrases are not equivalent, and we've clearly stated what we think the standard should be. But what we mean is we want evidence to suggest causality, and we've given examples of what that means and that's when we think they should be reported.

I know I keep saying this. Looking at the data that way is part of what is responsible behavior by a sponsor. If you just reflexively throw things over the wall, you don't find anything, you don't know anything. You're just tossing noise out. This is part of what a sponsor is supposed to be doing to protect patients—analyzing, looking at it.

Q: In investigator-initiated studies, what expectations are there of sponsor investigators to conform to the final rule, particularly conducting aggregate analyses, etc.?

A: (Corrigan-Curay) That's a difficult one. We expect all investigators to be able to comply with all the IND regulations, including IND safety reporting. But certainly they're not going to have all the data for an aggregate analysis, and in a single trial, there may not be enough events to really understand whether you've got an aggregate analysis. I think it's a little challenging there.

We would hope that, perhaps, with investigational products, investigators might also be in communication with the sponsor, if they are questions. But I don't think we have guidance, particularly on how to address the aggregate analysis, at this time. We recognize that they will have more limited ability to do that, and they probably will have fewer events to detect it.

Steven Beales, SVP, Scientific and Regulatory, WCG

Steven Beales is the Senior Vice President & Market Owner of Safety Reporting at WCG. An expert in the field of safety reporting technology, Mr. Beales has 25 years of experience in IT, and has spent over 16 years in the pharmaceutical industry. He joined WCG's ePharmaSolutions in 2009 and led implementation of the company's Safety Reporting Solution at Genentech across 100+ countries. In 2015, he led creation of WCG's SafetyPortal which includes a data-driven rules engine configured with safety regulations from those countries, which saved one organization hundreds of millions of dollars in the years since adoption. Over 200 million safety alerts have been distributed by these solutions via the cloud.

Dr. Robert Temple, M.D., Deputy Center Director for Clinical Science

Dr. Robert Temple serves as CDER's Deputy Center Director for Clinical Science and Senior Advisor in the Immediate Office of the Office of New Drugs (OND). As the senior advisor, Bob is a consultant to the OND director and other FDA officials on matters related to clinical program objectives.

Dr. Temple has a long-standing interest in the design and conduct of clinical trials. He has written extensively on this subject, especially on choice of control group in clinical trials, evaluation and active control trials, trials to evaluate dose-response, and trials using "enrichment" designs. He has been involved in the development of many International Conference on Harmonization (ICH) guidelines and numerous FDA guidances, including ones on study enrichment and on issues related to the design and interpretation of non-inferiority studies.

Dr. Jacqueline Corrigan-Curay, J.D., M.D., Director of CDER's Office of Medical Policy

Dr. Corrigan-Curay serves as Director of CDER's Office of Medical Policy (OMP). As Director of OMP, she leads the development, coordination, and implementation of medical policy programs and strategic initiatives. She works collaboratively with other CDER program areas, FDA centers, and stakeholders on enhancing policies to improve drug development and regulatory review processes.

Dr. Corrigan-Curay brings to the position a unique legal, scientific policy, and clinical background with expertise in risk and scientific assessment, and clinical trial design and oversight.

WCG's business process, global regulatory intelligence, and technology solutions lead to reductions of 45-55% of total SUSAR notification volume for our customers. This results in enormous annual cost-reductions in unnecessary site payments, monitoring time, site burden, and compliance issues.

WCG's typical business case for adopting our solutions:

If your organization sends….	Then your organization can save…
100,000 safety notifications per year	$500,000 per year
500,000 safety notifications per year	$2,500,000 per year
2,500,000 safety notifications per year	$12,500,000 per year
5,000,000 safety notifications per year	$25,000,000 per year

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