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A Fresh Perspective from the FDA

The Challenge of Overreporting

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 SUSARs and the impact on patient safety. This whitepaper is based largely, but not solely, on that conversation.

Since that conversation, the FDA has issued new draft guidance, Sponsor Responsibilities—Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies. Our experts are reviewing the guidance and will be sharing their insights soon.

More than a decade ago, the FDA issued its long-anticipated Final IND Safety Reporting Rule. It attempted to address the major problems sponsors and investigators faced with safety reporting.

It didn't solve the problem of overreporting. Now, in 2021, overreporting is worse than ever. Rather than the expected 90% reduction in IND safety reports, the FDA and sites continue to receive more IND safety reports every year, Beales said.

Sponsors must do a better job analyzing suspected adverse events before sending out SUSARs. That's not up for debate. The industry and regulators agree. "If you just report everything, you might miss something important. That could be a disaster," said Temple.

Anxiety and Overreporting

From the sponsor perspective, fear of noncompliance drives much overreporting, Beales said. Temple conceded that anxiety plays a role, but he contended that the primary reason is that safety analysis is difficult.

Regardless of the reason, sending a report that doesn't fit the criteria wastes of everybody's time, he said. The FDA wants a thorough analysis of the events that find the things that *matter.* "If there isn't a serious analysis, you're not really protecting the public or protecting patients the way you promise to."

Overreporting places a burden on the sites that must review all of their sponsors' reports and determine which ones need to be passed on to the trial's IRB. Providing the required analysis would relieve this burden. But do sponsors have adequate resources?

Beales raised doubts. Sponsors want to uphold their safety obligation, but only the largest sponsors with the scientific expertise and large pharmacovigilance departments, have been able to. Small and mid-size ones have struggled.

The FDA also expects judgement and discernment from sponsors—of all sizes. A small company with no safety experts would benefit greatly by putting together a safety assessment group. "This is a fundamental requirement of a sponsor to monitor safety. If they don't do it this way, they're not engaging their responsibility," Temple said.

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The Role of the Safety Assessment Committee

To provide this analysis, FDA encourages, but does not require, the use of a safety assessment committee (SAC). SACs sort through the safety data and determine, based on the evidence, what must be reported, explained Corrigan-Curay. SAC members, selected by the sponsor, review unblinded safety data and make recommendations regarding whether that information must be reported. It can include internal and/or external medical experts.

Large pharma companies typically create a SAC using medical staff from other programs. However, smaller companies—such as an emerging biotech with a single product—will likely need to outsource that function. Their medical staff would have a conflict of interest

in performing unblinded reviews of a program in which they are involved.

Another option to use the existing Data Monitoring Committee (DMC). While a SAC is distinct from a DMC, a DMC's expertise and reports can be used to facilitate operations of the SAC, Corrigan-Curay said. But members need to be clear on their roles. This can prove challenging, given that the DMC typically focuses on 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," Temple said. The committee members need the appropriate competency to look at the accumulating data. They must be knowledgeable about safety and related issues, and they need to be able to do the 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."

Corrigan-Curay agreed. The DMC must distinguish between operating as a DMC and as a SAC. Members need to keep in mind they aren't doing the risk/benefit analysis in terms of whether their trial continues. They probably need training to make sure they are answering the right questions, she added. "Are they applying our standards and asking 'Is there evidence to suggest this event is related?'"

It's less about how you do it than the fact that you do it, Temple said. "All this stuff that doesn't really look like an adverse effect of the drug, is a waste of everyone's time, especially the investigator's time. They *do* have to read them."

All About the Judgement: Aggregate Analysis

FDA developed its 2015 draft guidance, Safety Assessment for IND Safety Reporting, to facilitate evaluation of events requiring aggregate analyses. It notes that the determination of a relationship is a complex judgment, and not a simple application of a planned statistical analysis.

The guidance provides recommendations on an array of issues, including aggregate analyses for comparison of adverse event rates across treatment groups.

For example, the FDA introduced "suspected adverse reaction" to replace "associated with use," which is a broader concept. A suspected adverse reaction is one for which there is a reasonable possibility that the product caused the response, explained Corrigan-Curay. This represents a change from "a relationship cannot be ruled out," which could make almost anything reportable. You really need to think about whether there is evidence and what that evidence is.

She pointed out that the FDA provides examples of what evidence suggests a causal relationship:

- Events that are uncommon and associated with drug exposure (e.g., angioedema)
- Events not commonly related to drug exposure but are uncommon in the population (e.g., tendon rupture)
- An aggregate analysis of specific events observed in a clinical trial (e.g., known consequences of the underlying condition) that indicates those events occur more frequently in the drug treatment group than in a control group

Aggregate reporting requires a thoughtful multidisciplinary (e.g., scientific, statistical, and medical) approach, she explained. “Clinical judgment is key, so it’s not a statistical point that it gets reported. Really, it needs to be thought through. We provide in the guidance some of the things to think about.”

Temple drove home that point “We do not want to hear about every serious event, especially something that happens in the population, even without the drug. Sponsors need to analyze the rate of these events in the treated and the untreated group and then submit the aggregate analysis.”

Understanding causality is essential, and it can be confusing. For example, some see a possible contradiction between safety reporting guidelines offered by the International Council on Harmonization (ICH) and the FDA’s regulations, Beales said. ICH E6, the guideline on good clinical practice, says

an event shall be reported if a "reasonable possibility" of causality cannot be ruled out, but FDA requires "evidence to suggest a causal relationship."

There is no contradiction, said Temple. "Those two phrases are not equivalent," Temple responded. The FDA wants evidence that suggests causality. "Looking at the data that way is part of responsible behavior by a sponsor. And that's how you find things. This is part of what our sponsor is supposed to be doing to protect patients: analyzing, looking at it."

ICH E6 confusion may be the least of global challenges.

Global Standards, Global Headaches

As discussed, sponsors often struggle to meet the FDA's safety requirement. It's no surprise that it's even harder to meet the requirements of several countries.

The lack of global regulatory harmonization compounds overreporting, and according to Beales, it's the single biggest headache for pharma execs. "We've seen at least 40 different approaches to handling SUSAR distribution, and it changes regularly." Similarly, IRBs and ethics committees have varying requirements. Many sponsors lack the regulatory intelligence required to adhere to each country's rules. So being overly cautious, they overdistribute.

"Let's say we have patients who are bleeding severely, and we're into the aggregate analysis. We're continuing to get events, and we're sending reports off to Europe, Japan, etc. Sponsors lean toward sending reports to the FDA, just in case," Beales said. "'Better to send than not send,' is a prevailing view in the industry."

That may be the prevailing sponsor view, but it's most certainly not the FDA's view, Temple said.

The threshold can be debated, he conceded. "Do you need nominal significance or is a good, strong mean enough? Those are judgment calls." But the mere fact that, for instance, someone had a heart attack isn't necessarily reportable. "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."

Regardless of what Japan wants or Europe requires, the FDA wants sponsors to do a serious safety analysis before sending out reports, and it wants those reports to meet its specific requirements. But for sponsors to do this for international trials, they need to distribute safety information in a globally compliant, centralized, and automated way, Beales said. And that, he added, is a struggle.

Continuing the Conversation

The FDA recognizes the challenge. "There needs to be greater dialogue about why

[events] are being reported if they're not useful," Corrigan-Curay said. "You're communicating to us that the current guidance hasn't done everything we needed it to do."

Temple, too, sees it as an ongoing conversation, especially in terms of clarifying why overreporting creates extra work that could interfere with learning about events that matter. "And I think that's our most important and most critical argument. And that's the one that I think we should be prepared to talk about."

About Steven Beales

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.

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