



Episode Title: Sponsor's Role in Regulatory Testing -- A Conversation with Lara Hall

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Lynn L. Bergeson (LLB): Hello, and welcome to *All Things Chemical*, a podcast produced by Bergeson & Campbell, P.C. (B&C[®]), a Washington, D.C., law firm focusing on chemical law, business, and litigation matters. I'm Lynn Bergeson.

This week, I welcome to the studio Lara Hall, Senior Regulatory Scientist and Quality Assurance Specialist here at B&C and our consulting affiliate, The Acta Group (Acta[®]), to discuss the critical importance of understanding the role of the study monitor. As our listeners may know, chemical data -- this includes testing results, chemical studies, exposure information, environmental fate and monitoring data, to name a few -- are the new currency of the chemical community. These data are incredibly valuable, often proprietary, and increasingly used both to support chemical applications and to rebut allegations of adverse consequences resulting from chemical exposure. How these data are developed, who serves as study sponsor, how the sponsor interacts with the study monitor, the laboratory, and others are all significant issues and subject to Good Laboratory Practices (GLP) standards. Lara and I discuss GLP and the rights, duties, and obligations of all of the actors involved in chemical testing and offer some tips and insights in managing this increasingly complicated space. Now, here's my conversation with Lara Hall.

Lara, I am so pleased that you are here with us today to talk about something that is of enormous interest to our listeners: regulatory testing, and GLP, and the role of study sponsors. Thank you for being here.

Lara A. Hall (LAH): Thank you for having me, Lynn.

LLB: Before we begin, I mentioned in the intro that chemical test data was really the new currency in the chemical community. What I'd like our listeners to know a little bit more about is your background, how you came to be the leading expert on laboratory testing standards that you are. What can you tell us?

LAH: I began my career in the field researching nutrient transport, metabolism in freshwater streams. I led a team in a multiyear, multi-site project that was funded in part by a Safe

Drinking Water Act grant funded by the New York State Department of Environmental Conservation (NYS DEC) and the U.S. Environmental Protection Agency, or EPA. One of our reporting requirements of the grant included a quality assurance project plan that involved comprehensive and regular field laboratory and data audits by a quality assurance professional, much like myself now. There's a general acknowledgment that quality published literature must not only stand up to the rigors of independent peer review, but fundamentally also must demonstrate data integrity through the scientifically sound test design, standard methods, and appropriate quality controls and assurance measures.

Our field and laboratory research aligned with these principles, but this was really the first project that I was involved in that integrated and deployed a quality management system as a critical part of the project plan. Through this project, I saw firsthand how the improved quality culture transformed our research facility's overall approach to field preparations, data generation, documentation, multi-site coordination, personnel safety, systematic review, and also reporting. With a newfound appreciation for quality assurance, my career then took an unexpected 90-degree turn toward regulatory consulting, and in 2003, I hung up my waders. Since then, I have been assisting clients in the chemical industry, meeting their regulatory and quality compliance needs.

LLB: That transition certainly has benefited us, Lara. I know what you do, and I know for whom you do it, but maybe you can explain to our listeners what is your day like? What types of regulatory consulting, and data development, and GLP standard advice -- what do you do? For whom do you do it? Just give us a little color there.

LAH: Our clients are composed of small and medium enterprises or SMEs, large commercial chemical manufacturers, producers, formulators, and also consortia that are formed by these entities with a common goal. For example, they may be responding to test orders under Section 4 of the Toxic Substances Control Act, or TSCA, addressing data gaps in environmental, occupational, and consumer exposure. The data are required for risk evaluation, or they may be collaboratively meeting other advocacy objectives. The ways in which I support clients, I would say vary significantly from project to project and day to day, but most of my activities involve placing, monitoring, and quality assurance studies to assist with regulation -- excuse me, registration -- of new chemicals, pesticides, and biocides.

Most of the testing support that I provide focuses on evaluating existing data and developing and executing test plans to develop new data that may be required to obtain, maintain, or even defend chemical registrations globally. My area of expertise is in environmental fate and effects and quality compliance. But as you know, regulatory testing programs typically require data on product chemistry, toxicology, efficacy, and exposure, so I often facilitate collaborations with other subject matter experts and regulatory specialists within our firm and our clients' organizations, as well as testing facilities, to generate data, and attorneys like yourself, who advise on a lot of enforcement and compliance matters, contracts, and data compensation. The regulations driving our research that we support are ever changing, so we have to keep up to date on harmonized testing guidelines, industry standards, data requirements, and accepted alternative methodologies -- and perhaps computational models -- to ensure that the data that we help to generate are scientifically meaningful and compliant.

LLB: You just covered an awful lot of real estate, Lara.

LAH: Yes, we're pretty busy.

LLB: I know you are extremely busy. We've got all of these TSCA Section 4 test rules. We have chemicals that require -- or are better off having -- some data supporting applications under new chemicals. We have FIFRA [Federal Insecticide, Fungicide, and Rodenticide Act] data supporting data call-ins -- you name it. With this Administration, the Biden-Harris Administration -- and its commitment to data quality and data integrity, it seems to me that there are few issues that we tackle here at B&C and Acta that don't involve understanding the value of data, generating those data, being mindful of not just the jurisdiction in which the data are being generated, but how can those data be the gift that keeps on giving, right? So we want data investment to be monetized over time and to serve the clients' regulatory needs in multiple jurisdictions. You do all of that, right? You counsel on the regulatory side, but also on generating data that are compliant with GLP and other testing standards. That's just a huge order.

LAH: Yes, but I think there's a place for both of those needs. I mean there's doing the science right, and then there's doing it in a way that ensures that the data are reliable, reproducible, and relevant. Those three Rs really drive a lot of what I do. Sponsors come to us (or clients come to us) with either, as I said, existing data or a need to develop new data, and we need to figure out what's the best path forward. That's not always going to be a one-path track. Sometimes it's meeting the needs of one or multiple stakeholders for a variety of needs, and we have to think not only in the immediate term, but we have to think longer term about how these data might be used and the integrity those data need to stand up through the test of time, the actual raw data need to stand up through the test of time, and we need to protect the investment of our clients in developing those data --

LLB: -- because they're not cheap.

LAH: That's true.

LLB: Most of these studies are super expensive. Let's talk a little bit about GLP, Good Laboratory Practice standards. I think there's a good deal of confusion about what these standards are, why they are important, and whether if EPA demands data, for example, through a TSCA Section 4 test rule or through, say, a new chemical application under TSCA, must these data be generated according to GLP standards? Is that required? Is there a downside if they're not required? What can you tell us there? Because this is an area of tremendous confusion that I have sensed over the years in our clients' questioning.

LAH: At their core, GLP standards offer a basic guide for ensuring reliability and reproducibility of the data that inform regulatory risk and mitigation decisions by various agencies, including EPA, FDA [U.S. Food and Drug Administration], and so forth. The addition of GLPs to regulatory law has occurred, I would say, relatively recently in the history of chemical and drug industries. Just for a little bit of context for our listeners, I'd like to share just a brief history -- and I promise it'll be brief.

By the mid-1900s, the world saw a significant increase in the amount of toxicology testing in response to the development of drug companies and dispensaries, and guidelines were developed to support the evaluation, regulation, and registration of chemicals and drugs. But there were no definitive regulations set forth by the FDA or EPA at that time. FDA was performing inspections of companies' in-house and testing facilities and commercial laboratories to assess the validity of test results. It became apparent that the industry lacked a unified and systematic practice for ensuring data quality. FDA identified significant quality concerns: inconsistencies and questionable -- even fraudulent -- scientific and animal welfare practices. So in 1979, the U.S. government enacted regulations to prevent this

misconduct, and that outlined enforceable standards for what are considered today to be lower-case good laboratory practices.

The FDA GLPs were codified into law under the Code of Federal Regulations (21 C.F.R. Part 58), and then later in 1984, the EPA GLP standards were enacted under the Federal Insecticide, Fungicide, and Rodenticide Act, or FIFRA, and TSCA, cited under 40 C.F.R. Parts 160 and 792, respectively. When these standardized and enforceable principles are followed, the idea is that regulators should be able to trust the study data being produced. Study conclusions and chronology can be substantiated based on the written record, and the integrity of the data is insured, such that the data can be reviewed for long periods of time after study completion and due to the archiving requirements built into GLP. Not all of the regulatory testing is conducted in accordance with GLP, however. Within the GLP regulations, there's this acknowledgment of exceptional cases and study designs that do not require GLP compliance. Exemptions can include specific physicochemical properties tests, computational models, high-throughput screening assays, exposure monitoring, and discrete study phases in peer-reviewed published literature. Generally speaking, the expectation is that nonclinical health or environmental safety studies submitted to EPA and FDA should be conducted in accordance with GLP. Otherwise, a very good justification is required. It comes with some risk of reduced reliability and possibly study rejection if GLPs are not followed.

LLB: All right, that makes sense. Do you have standard advice? Do you basically take the position: just go the GLP route because you're assured of a better reception in the regulatory body where the data are being relied upon?

LAH: I think that is the general understanding and principle behind it. Even if you're not following capitalized Good Laboratory Practice standards, following good laboratory practices, it's just a good commonsense practice that underpins the integrity of your data that you're generating. We'll talk a little bit about some of the factors that make GLP testing unique and the roles and responsibilities within that that, I think, help to solidify that principle.

LLB: Let me ask a question that I probably should know the answer to, but I honestly don't. We have OECD [Organisation for Economic Co-operation and Development] GLP standards. We have EPA GLP standards, as you noted, under 40 C.F.R. 160 and 792, respectively, and FDA GLP under Title 21 of the C.F.R. Are all of these largely the same, or are there subtle differences of which listeners should be aware?

LAH: They are very similar. They are meant to be harmonized, and because of the way that they rolled out in chronology, as I mentioned, and sort of the history of the GLP, they built upon each other. And so with OECD, which is the Organization for Economic Cooperation and Development, they established Principles of GLP in the European Union (EU) in 1981, so between when FDA and EPA rolled out their GLPs. These principles were developed to address the generation of data quality, supporting regulatory decisions with an acknowledgment that the data were being relied upon globally under multiple regulations, and so harmonization was one of the objectives with OECD principles. They align very closely with FDA and EPA GLPs. There are some subtle, and perhaps not so subtle, differences that are more geared toward select terminology for comparable study roles, functions, and defined study milestones. But studies conducted in accordance with FDA or EPA GLPs are considered compliant with OECD GLP because of the global harmonization effort.

LLB: That's a good thing.

LAH: It is, very much so. And unlike many other OECD countries that adhere strictly to OECD GLP, the United States does not certify the GLP compliance of laboratories under its inspectional and enforcement jurisdiction. This is really important. This is a sort of misconception by many sponsors who are entering into this kind of testing and trying to figure out: Which lab do I use? How do I know who is compliant and who's not? Are they asking for a certificate? I would say most, if any, of the labs in the United States do not have certifications of this type, unless they have actually been inspected by an outside quality assurance monitoring authority under OECD, which is pretty rare.

The harmonization of GLPs under OECD allows multiple countries to accept data from other OECD countries through the Mutual Acceptance of Data (MAD) system. The MAD is a multilateral agreement that allows OECD countries, the United States included, and other adherents to share and accept results from non-clinical testing if the basic criteria are met. This reduces duplication of data, saves industry and governments time and money, and reduces the use of animals in testing. The governments participating in the MAD system have confidence that chemical safety test data generated in other countries are reliable if the study complies with the OECD standards for testing and data quality or its in-country comparable.

LLB: Everything that you said, Lara, makes perfect sense. There is this -- for lack of a better word -- intellectual construct that allows data in OECD member countries, EU, United States to generate data that adhere to kind of some guidelines with regard to data quality and how the data can be generated and shared in multiple jurisdictions, so that's great. We're probably talking a little bit about what things might go wrong in this construct. But you've mentioned a number of entities: the study sponsor, the laboratory study monitors. I'm getting the sense that, within this construct, there are various actors, and everybody has a role to play, everyone has a lane to swim in. What are the primary roles under GLP and the primary obligations of each of those actors?

LAH: I like to think of the key roles within GLP testing as the four pillars that maintain the structural integrity of the quality system. The testing facility management is responsible for ensuring that there are sufficient and appropriately trained personnel. They assign the role of Study Director, and they ensure that there is a Quality Assurance Unit (QAU), and they verify that test and control substances are appropriately tested. All of this is spelled out in GLP standards. The Study Director has the unique role as being the single point of control in a GLP study and is responsible for the overall conduct and compliance of the study.

The QAU is the third pillar. It's designated by TFM, or Testing Facility Management, and it performs duties relating to quality assurance of the studies. They perform study-based inspections, as well as routine process-based and facility inspections, and they issue their inspection reports to both the Study Director and TFM. GLPs define the fourth pillar, the Sponsor, as the person or entity who initiates and supports the study, financially or using other resources. It may be a person or entity who submits the study to EPA in response to an application, permit, TSCA Section 4 test rule or Consent Agreement, or a TSCA Section 5 rule. It may be that the Sponsor is also the testing facility, if it both initiates and actually conducts the study.

There are numerous other personnel involved in GLP testing who have various tasks throughout the life cycle of a study, including, for example, animal husbandry, culture technicians, analytical chemists, pathologists, veterinarians, statisticians, and archivists. In a multi-site study, Principal Investigators act on behalf of -- but still under the direction of -- the Study Director during discrete assigned study phases.

LLB: I'm kind of guessing that GLP standards help define the do's and don'ts and how each of these entities relate to one another. For example, if you're the Study Director, can you just unilaterally speak with any of these other entities, including the Study Sponsor? Or are there rules of conduct that, maybe not prohibit, but strongly suggest that you swim in your own lane to avoid role confusion and conflation? How does that work?

LAH: In terms of communication channels? Yes, there are definitely lines of communication, and we like to see at any testing facility that is conducting GLP testing that they have clear roles and responsibilities delineated and that they have appropriate reporting channels. Because the Study Director is the single point of control, they can absolutely reach out to the Sponsor or to QAU or to TFM to address issues as they arise. But really, the responsibility lies with that person. That individual is assigned by TFM. Where lines -- in my experience -- where lines tend to get blurred are when a Sponsor is doing in-house testing and serving as the testing facility, or in small testing facilities, where a single person may wear multiple hats in the course of a day, in the course of a year. And when we think about the roles and responsibilities of GLP and I say that there needs to be a clear definition of responsibilities and roles, that's within the context of one study. A Study Director's directing the study, TFM is providing the resources, and QAU is working independently, is not engaged at all in the study, and is ensuring that all of the rules are being followed. They're the watchdogs to make sure that everybody's following the rules and swimming in their lane. The Sponsor needs to stick very, stay very carefully and intentionally, within their lane in terms of its support of a study, but absolutely under no circumstances should they be directing the outcome of studies, nor should they be directly involved in study conduct, with the exception of some study phases where the Sponsor can uniquely provide services in generating the data, and that is spelled out in a study protocol. Again, that role, that function is very specifically detailed so that everyone knows their role to play.

LLB: This sounds -- it probably sounds easier than it is. The role that I think we most frequently find ourselves here at B&C, Acta, and our third organization, B&C Consortia Management, where we manage maybe some two dozen or so chemical consortia, many of which generate data in satisfaction of regulatory mandates of one sort or another under FIFRA, or TSCA, or some other initiative. More often than not, Lara, unless I'm mistaken, the consortium would be the Study Sponsor, could be 10, 15 member companies that get together and agree to discharge a data need that has been identified by, say, EPA or some other authoritative body. Everybody is paying for that study. How are the Study Sponsors' obligations communicated? And how do you manage the relationship between the Study Sponsor and EPA, for example, in this hypothetical that is assessing protocol for a study. There might be some back and forth between the study sponsor and EPA on what's the best way to get to Yes, especially in areas where how to generate the data, and what type of study is being done, may not be all that clear? How do you sort all of that out? What is your role in all of that?

LAH: Let's start with what's driving the study to begin with, and that's the study protocol. When data need to be generated, and if GLP compliance is required, it starts with the development of that protocol or that study plan. One of the fundamental requirements of GLP, whether it be FDA, EPA, or OECD, one of the very explicit requirements of a Sponsor is that the Sponsor approve that protocol. Now, whether that occurs through signature of that protocol or not, there are different interpretations about that that we could talk about. But fundamentally, the Sponsor must approve that protocol, and it must be signed by the Study Director. In some contexts, depending on the data need, if EPA is involved, it may be that that protocol is submitted to EPA as well for review and approval prior to the approval of Sponsor and Study Director. That ensures that, first and foremost, that the Sponsor and the

Study Director are on the same page as to what study needs to be conducted, how it's going to be conducted, the regulatory requirements to ensure that the regulatory and testing objectives are being met, and that everyone understands their roles and responsibilities. The study protocol sets that in stone for all intents and purposes.

Any departure from that protocol must be documented by amendment. Or if it happens after the fact -- it's an oops -- then it has to be documented as a deviation. The key with GLP is that whatever occurs in a study must be documented, so when we're looking at that protocol, we're finding ways to bring closer to center the understanding by both the Sponsor and the Study Director as to how we're going to go about this testing. Again, to the extent that that's required or appropriate, it may be that the regulatory authorities are also involved. But under no circumstances should a regulatory authority or a Sponsor insert themselves into the study in a manner that could create even a perception of -- let alone in actuality -- a situation where the course or the conduct of a study is being influenced unduly by an outside entity. It should be directed only by the Study Director.

LLB: Mm-hmm. In your experience, Lara, because you've been doing this for years now, what are the responsibilities, rights, duties, and obligations of these various parties that are most often overlooked and might cause problems that could invite questions as to the reliability or the integrity of the study, or deviate from the protocol in a way that could compromise the entire mission? What could go wrong in this fact pattern?

LAH: When we think about the overall life cycle of a study, prior to study initiation, which is, as I said, when the protocol is approved by -- importantly, the Study Director, but also has approval of the Sponsor and if appropriate, EPA -- there are several critical decisions regarding study objectives, scope, and study placement. This happens before a Study Director is even assigned. Then throughout study conduct, reporting, auditing, archiving, and the registration process itself, the Sponsor may have discrete functions to ensure the timely progress of a study and the validity of that study. The Sponsor ultimately bears the responsibility for determining whether and when to submit the study data to a regulatory authority to support a registration, application permit, consent order, or what have you.

Responsibilities associated with three critical studies, types, and phases immediately come to mind when I think about where things might go wrong. In my experience, we find that study placement can stress the process and can slow things down. If we don't put a lot of thought into how studies are placed, things can go sideways. Protocol or study plan approval, as we've just discussed, is another important step where things can sometimes go wrong, and test substance characterization. The Sponsor should ensure that the Testing Facility that they select for conducting the testing is able to conduct the study in compliance with GLP, and that importantly, the Testing Facility is aware that the study is to be conducted in accordance with GLP. That seems like an obvious --

LLB: Yes.

LAH: -- no-brainer for the study, but if this isn't stated explicitly at the beginning, that can lead to a lot of questions and problems down the road. That disclosure is absolutely critical for establishing the regulatory quality, context, and expectations -- and ultimately the scope and cost of the study. The turnaround times and cost are often driving factors in a Sponsor's decision-making when considering whether to conduct a study in-house, if the resources permit, or engage a third-party contract lab. If a Sponsor is considering going down the path of the third-party lab, they have to consider laboratory capabilities and capacity, as well as the laboratory's quality management system to ensure compliance. Once a Testing Facility

has been selected for study placement, significant effort must be expended then to negotiate contractual terms for testing services and to maintain the confidentiality of the data or the information that's being generated or supported in the course of study conduct. So it's really important, as you embark on just the study placement phase of this, that you review these agreements carefully.

Commonly, study protocols and contracts -- there are discrepancies between those. Where we see that occur most often, again, seems like a simple, obvious thing to check, but the Sponsor identity and address. If those aren't consistent, that can lead to a lot of confusion about roles and responsibilities. Who is the lab going to contact? Archiving location. That's often in both the protocol and the contract, and usually, they don't agree, so we step in often and have to identify these discrepancies, maybe even the duration under the original contract for the archiving term that is covered by the study cost, sample specimens disposition: What are you going to do with the samples at the end of the study? The period of time after the draft report is issued without ongoing communication with the Sponsor before this Testing Facility just moves forward with issuing a report in final. If the Sponsor wants time to review a draft report, that needs to be agreed upon up front; that could lead to a lot of confusion.

Again, as I said, protocol approval. There are lots of interpretations about who signs when, and that needs to be worked out with the laboratory as well. Sponsors should absolutely take the opportunity to review a protocol in draft for clarity, completeness, and compliance with the relevant testing guidelines and GLP standards. This is really that opportunity to ensure that the Sponsor, and the Testing Facility, and the Study Director, specifically, are on the same page regarding how the study will be conducted. Unless there's an appropriate justification to deviate, the studies should comply with all relevant testing guidelines and GLP recommendations. So understanding either the Sponsor's or the Testing Facility's rationale for deviating from any such guidelines or GLPs, that really does need to be written into the study protocol, again, just to make sure that everyone is on the same page.

When we talk about the second example that I gave -- testing substance characterization and stability -- that's when you start to get into the flow of the testing program, the initiation of the study. Before any test substance is used in a GLP study, it must be characterized. That is a requirement of GLP. But it's not necessarily the Sponsor's responsibility to do that. There are several considerations for Sponsors engaged in critical characterization and stability activities in GLP testing. If the Sponsor supplies the testing material, typically what we see is that the Testing Facility relies upon the Sponsor then to provide or confirm the location of methods of synthesis or fabrication. How did the sample come to be? What is in the sample? What's its composition? Documenting that in a way that demonstrates a knowledge and a suitability of what that sample is and the suitability for using that sample in GLP testing. That must be documented prior to use in the actual GLP study. Typically, that's in the form of a certificate of analysis, ideally signed and dated by the analyst, and it may include -- should include -- an expiry or a retest date. It may state the purity of the main constituent or the active ingredient, or it may summarize a full compositional analysis.

Oftentimes, Sponsors get bogged down with the order of operations and understanding its need to assist the laboratory in documenting what that sample is and making sure fundamentally that they're testing the right sample. That speaks to chain of custody, getting the sample from its source of origin: maybe the company that is manufacturing the sample -- or perhaps it's through its commercial supplier -- getting it from that source to the laboratory requires forethought, and it requires documentation. Understanding how to store the sample to preserve the integrity of the sample throughout the duration of the study is

important. How long is it good for? Under what conditions should we store it so that it doesn't degrade? If we're introducing it to a test system that requires like a formulation, how do we demonstrate homogeneity in the vehicle?

These are all fundamental aspects of study conduct that need to be addressed before you even begin testing animals or introducing the test material to the system, whatever that system may be. I think too often we have situations where Sponsors or Testing Facilities put the cart before the horse, and they don't get through those two critical phases of protocol development: contract negotiations to make sure that everything is laid out as to how the study will go, and then characterizing and demonstrating stability of that test substance. And should there be a need down the road for that sample to be re-characterized, there needs to be an agreement between the Sponsor and the Testing Facility of who is going to maintain a retention sample from that bulk batch or lot. There may be a question down the road as to the ultimate stability under the conditions of storage or conditions of study conduct, and there may be a need to go back and reanalyze it. Who's going to keep that sample, and under what circumstances, and for how long? These are all things that we assist our Sponsors in working through, ideally, before we get to the point of actually initiating testing.

LLB: There's just enormous amount of granularity, Lara, based on what you just said. I know everyone in the -- the actors -- are supposed to be working within this framework where everybody knows what they're supposed to do, and there's a seamless meshing of interest and actions, and nothing can go wrong. But I also see opportunities for things just going off the rails, because there's so much detail and so many people that might be involved, so caution is necessary. Constant monitoring is necessary. It's not like you have all the time in the world. You talked about shelf life and stability and the expiry of the samples' efficacy. All of these things have to work in tandem. No wonder you're as busy as you are. Plus you have, at any given time, lots of different studies ongoing, in furtherance of any number of regulatory, stewardship, or advocacy goals. How do you keep it all straight? Are there just enormous checklists and Excel spreadsheets that you go through and make -- could you give us an example of maybe just one thing that went off the rails that could have been prevented if everyone had observed their rights, duties, and obligations in this construct?

LAH: I think really it -- gosh, there are so many examples that come to mind, if I have to pick just one. Really, we subscribe to a chemistry-first mantra within our firm, and I think that's because so often if we move forward quickly with all of the other program administration pieces, and we forget the fundamentals of what are we testing and why, I think that's where things start to go off the rails, as you've said. I can think of instances where samples have been sent that were not appropriately labeled, and they've been mixed up. Or there has been an instance where what we thought we were testing was not as pure a substance as what was either intended or understood. And there were other impurities that can contribute to the toxicological effects. So as we start to interpret these data, not understanding what it is we're testing can lead to a mischaracterization of the actual toxicological profile of the pure substance. So while I can't share specifics about that, that is an example where I have seen this issue of test substance characterization, if not done well and timely, can lead to many problems down the road. You can imagine the number of headaches that can arise from a mischaracterization of a potential hazard and risk for a substance.

Another example may be that, in commerce, we often see these substances in a formulation where there may be inerts, there may diluents, there may be stabilizers that contribute to the shelf life of that commercial product. But when we test substances for these regulatory purposes, nonclinical or preclinical toxicology or environmental fate and effect studies, we

generally tend toward testing with the active ingredient, so it's discretely tested. It's not in that formulation that I described with inserts and stabilizers. That means that you face many challenges with isolating -- in the context of GLP testing -- isolating the behaviors of that substance, and it can be very challenging. Again, knowing what you're dealing with, first and foremost, and ensuring the integrity of that sample during the course of the study is really crucial. Yes.

LLB: You sounded like you were beginning to answer my penultimate question, and that is, what are the key takeaways from our conversation that you really wish listeners would focus on when thinking about GLP and conducting testing generally as a Study Sponsor?

LAH: I think there are a few things. There is a place for non-GLP testing in research and regulatory science, but compliance with GLP for non-clinical human health and environmental studies is required to support OECD regulatory requirements, and that includes the United States. Studies conducted in countries that are not signatories of the MAD agreement may not be considered by EPA and FDA, even if conducted according to OECD testing guidelines or under that specific country's quality compliance system. I would strongly advise that entities should not claim GLP compliance if the fundamental requirements of GLP have not been met. Doing so can lead to significant enforcement risks. It is critically important that the Sponsor understand the scope of the study, and the terms, and that these align in both the contract and the study protocol, as I've said. It's very important that the Sponsor understand its role in study conduct, and that it's inherently limited, and intentionally limited, by GLP.

LLB: Lara, you've done a masterful job of outlining in broad strokes the complexity of this space. We do so much study generation monitoring, arguing with EPA, or ECHA [European Chemicals Agency] with REACH [Registration, Evaluation, Authorisation and Restriction of Chemicals regulation] data, on the suitability of data to fit a particular need. I can't begin to express how grateful we are for you, because you're part of the team here and provide invaluable counsel, expertise, and judgment on some very, very tricky issues that will only increase over time, because there's so much testing going on right now: for TSCA purposes, REACH purposes, PFAS [polyfluoroalkyl substance] purposes, you name it. Maybe you can direct our listeners to areas where they might find additional information, because in our 45 minutes of conversation, we've only just begun that conversation. Where can listeners find more?

LAH: The predicate regulations, I think, are an important place to start. The U.S. GLPs are published in the *Federal Register*, 21 C.F.R. Part 58 for FDA and 40 C.F.R. Parts 160 and 792 for EPA FIFRA and TSCA, respectively. OECD recently overhauled its website, so finding the harmonized test guidelines and principles of GLP, even the criteria for MAD may be a bit challenging, so I would encourage listeners to refamiliarize themselves with these OECD resources and update their web links. Additionally, OECD has published several advisory documents that supplement, clarify, and aid in the interpretation of OECD principles of GLP. Most relevant to our discussion today would be advisory documents number 11, regarding the Sponsor's role in GLP testing, and number 19, regarding test item characterization.

Additionally, if listeners are feeling a bit overwhelmed by all of the requirements for regulatory testing and unsure where to start, I would encourage them to visit our website at lawbc.com, where we share extensive knowledge, insights, resources, and even training programs. In fact, I believe we just posted a link to our June 13 webinar: The Sponsor's Role in Regulatory Testing -- Complying with GLP Standards. That's available as well.

LLB: I want to emphasize how much information is in that listing for the June 13 webinar: It was the webinar slides, the actual recording of the webinar, a list of additional resources, and a very helpful Q&A document that we fielded questions from our very large audience. Many of the questions they asked may be floating around your own head right now listening to this podcast.

Lara, I want to thank you. I thank every day that you are part of the team here because of your precision, your expertise, your vast knowledge, and all that you bring to our clients in helping them navigate this very, very -- I think -- challenging space. Your expertise is absolutely invaluable. I've really enjoyed the conversation.

LAH: Thank you, Lynn. It's been a pleasure.

LLB: I hope you have enjoyed my conversation with Lara on chemical testing and the role of GLP standards. Lara is, I think, as you all can tell, a true expert in this area. We hope our conversation has demystified this complicated but very important area.

All Things Chemical is produced by Jackson Bierfeldt of Bierfeldt Audio LLC.

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