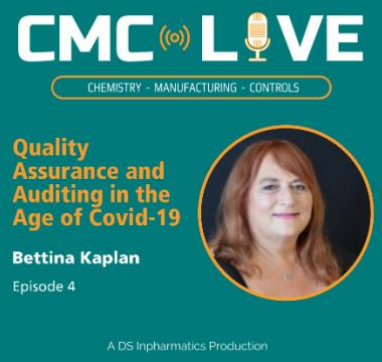
Quality Assurance and Auditing in the Age of Covid-19

Episode 4



Ed Narke
Welcome to CMC Live, everybody. Today's guest is Bettina Kaplan. We're talking to her about quality assurance, and more specifically, audits. Bettina lives in Boca Raton, Florida, and has worked with DSI for several years. I've known her before that through our network, and she is a great Senior Quality Assurance Consultant here at DSI. Lesser-known facts: she has three exceptional children and is a New York Mets fan. The truth is we went to a Mets spring training game. I think it was March 5th, right before the shutdown. We spent some time in the outfield talking about this, actually, the podcast today. Today. we're talking about some of the current events out there. The FDA has halted most in-person inspections during the COVID-19 pandemic, audits have stopped, some are still being performed, or some will ultimately be performed differently. It's a challenge but this is part of the evolution. Things have always evolved and always will. We kind of wanted to talk about GMP audit alternatives during the COVID-19 pandemic or any disruption, requesting, preparing for, or responding for the overall virtual audits. Also, how that might change in the future.

> "The person [auditor] needs to be able to communicate properly. So, build a rapport with the auditee. When you build that rapport, auditees tend to tell you more than just your basic questions."

Bettina is a seasoned pharmaceutical quality assurance compliance professional with years of experience at Sandoz, Hoffman-LaRoche, Purdue, Sharp Packaging. As I said, she has worked here at DSI for several years. Bettina, can you tell us how you got into QA and auditing?

Bettina Kaplan
I started out getting my degree in chemistry at Stevens Institute of Technology and went to Columbia Medical School to do some research. I had been planning on going from my MD. I decided that I didn't know if I could commit the time to become an MD. I started to apply to the industry and started at Schering-Plough as a Key Chemist. I worked in the analytical lab for three years and decided to do more and learn more. I wanted to know more, so I started in QA. I worked at a few larger Pharma for a couple of years in QA and then moved to Stewart Pharmaceuticals, where I started to get into auditing. I worked with a gentleman who had been at the Philadelphia FDA for a while, and he taught me a lot of things about auditing, the general FDA guidance, and the industry in general. From there, I started to move up in the quality arena. Well, that was in Delaware. I was getting married, so I had to move back up to New Jersey. I went to a company that was a virtual company, one of the earlier virtual companies. It was OTC products and some foods. We had roughly 40 suppliers, and all of them had to be controlled. They had to be audited, they had to be managed, and a system had to be built. I was

with that company for quite a while until they decided to sell the company to a major pharmaceutical company that bought the product. For the company, I had felt we had a great and excellent quality management system.

After that, I went to QA and Compliance at Roche, where I got heavily into the compliance. Roche had just come out of their self-imposed consent decree. My QA roles just kept increasing over the years as I took on new roles at new companies. I got intrigued with all the different aspects of quality and how quality was changing. I saw how many sites didn't understand what quality was about. You would go in, do your audit, and see how places needed your help. As an auditor, they would ask you for help to understand what's required. Audits can sometimes be a two-way street. From there, I just kept going up in quality in the industry. My last industry position was as a Senior VP of Quality.

Ed Narke
Okay, that's great. A lot of folks know about quality assurance but tell us a little bit more about audits. Types of audits, etc. for those folks either new to this podcast or for those not intimately familiar with the industry.

Bettina Kaplan
There are several types of audits; you have your supplier audits that are required by the FDA and by all the other regulatory bodies that we keep on top of our suppliers. What the suppliers mean, you could have suppliers of APIs, suppliers of raw materials or excipients, and you can have your CMOs that manufacturer, package, or test for you.

> "So, if you have to cover manufacturing, analytical and all the quality systems in one day to do a thorough audit, there's no way you can do it with just one person. You need to have the other experts."

To be on top of those suppliers and manage them adequately, you need to go out and see what they're doing. To do that, you set up your supplier audits. Lately, the industry has been going with risk-based audits, just like the FDA does risk-based inspections. It is based on compliance, meaning the compliance status to the site, how they've performed in the past, the criticality of the material they're supplying, any issues that you may have seen. So, you set up your schedule for audits, and it's an audit plan that you sign off yearly, usually where it'll say these are the sites to do for audits this year.

Are they for cause audits? For cause audits, it might be where you've had an issue with a site, and you routinely are going back to check on them, or it could come up sporadically as a problem arises. Then you have your routine audit, where you check on the site to make sure that you know what's going on. Has anything changed since last time? Or is it a new supplier? For new suppliers who want to get out, get into the plan to get a feel of what's going on at that site. Is it adequate for your work? Can they meet the requirements you have? Can they produce what you need? Can they do it in a compliant manner? When you go out and audit, you're looking at all these items as part of your audit.

Ed Narke
Okay, as a follow-up question, what are the top three skills that a quality auditor has to possess in your mind?

Bettina Kaplan
They need to use their eyes and look while they're going around. A lot of us see things differently when you see it through an auditor's eyes. An auditor, why does an auditor always find these things? Because it's something that gives you that gut feeling, you know, you have the experience, the knowledge of what needs to be in place, you know what the site should have in places versus some of the issues that you find. I want to say, "auditor's eyes,"

it's a hard thing to evaluate sometimes, but you can. Knowledge of your GMP or whatever regulations you're auditing against, ICH Q7, if you're doing a GxP audit, PCPs, etc.

Then the person needs to be able to communicate appropriately. So, build a report with the auditee. When you make that report, auditees tend to tell you more than just your basic question. Just like the FDA does, they try to build that repour so that people will continue to talk and not just answer the question.

Ed Narke
Okay, good. When we started, we talked about some of the inspections that typically happen, halted audits, on-site audits, and different elements that have been suspended with travel restrictions. Before we get too far down that path, can you tell us about some trends, major trends in quality auditing that you saw before the shutdown?

Bettina Kaplan
Well, yes, everybody has been moving on to risk-based auditing versus scheduling routinely every year or two because it's become complicated to get to all of the sites you need to. Sometimes you have limited resources. The other thing that you'll see is that companies are going out and looking for help with auditing. They're going to consulting companies or firms to offer that help, that extra person to go out and do an audit for them. A lot of the time, that's beneficial because the QA person working with a supplier has daily work with the supplier. They begin to lose objectivity when they go into a site because they know certain things and can't look at them from a fresh eye. Having new eyes go in separate from the company helps a company get a better audit.

Ed Narke
I've got a question if you don't mind. Being on the supplier side of this my whole career, I have a special place in my heart for audits. That being said, when you come in as an outside auditor, sometimes it's successful, sometimes it's not. How do you ensure a successful audit? If you're coming into a place where no one knows you, they understand why you're there. How do you establish that relationship early on? It's not easy.

Bettina Kaplan
No, it's not and, one of the things that I was just going to say before you brought up that question are the other things that need to be prepared. They need to know the site they're going into, maybe look up some of the people, try to see who is there, is there any connection? What has the FDA found? Try to look at it from, "is there any connection I can make?"

A lot of times, you'll find "Oh, I know someone there." You can hit it off by bonding that way. A lot of times, I feel it out when I get to the site. I will feel out everybody at the meeting. I'll feel out the QA person, of course, being QA, I try to bond with that QA person. It makes a big difference when you're doing the audit; if you can start to connect with someone on the audit team, it's looking and listening. One of the things you have to do is listen carefully to what they're saying. Often, you'll get a hint about how they want to move things along, if they're trying to hide anything, and what they say in that opening meeting. It's a natural feel. Some auditors are better than others, and it's various.

Brian Lihou
Yeah. Okay. I mean, it makes sense. I know, just in our time working together, we're often recommending to clients that more than one discipline is represented on an audit. How do you determine, going into an audit, especially as we're kind of getting into this virtual field where you want to get as much exposure to the issues in the plant as you can, and you're limited, how do you determine when it's good to have, let's say, "an analyst or a drug substance chemist or an aseptic processing person?"

Bettina Kaplan
The first way you can determine that depends on how many days they will allow you in the plant, how many days for the audit? If you have to cover manufacturing, analytical, and all the quality systems in one day to do a thorough audit, there's no way you could do it with one person. You need to have other experts. Now depending on the type of work they're doing: if analytical is minor, you may be able to get away without an analytical person, but if you're doing formal method development and all the validation, then you want to have an analytical person there. Also, if it is a difficult compound that you're working with or a product. For manufacturing, you're going to choose the expertise of the type of work performed at the CMO. It could be a person with aseptic or oral solids; it will depend on what is being produced at that site. You'll determine who the best technical representative that could join you is. The other thing is, you had problems at that site before, where have the problems been? Have you been in manufacturing? Has it been in the lab? Or has it been in QA? Based on that, you will say, "Okay, if we've had a lot of analytical problems, you want the analytical person; you may not have to have the production person." It is different, and it depends on the site themselves and their history with you.

Ed Narke
Okay, so we're in the summer of 2020 or the summer of COVID-19. So, things probably have changed. But then again things have already started changing prior to this all. Can you review some of the current audit landscape and some of these apparent challenges you've seen or foresee?

> "The other issue is going to an audit. If you're from a location like where I live, I have to be in quarantine for two weeks before I can even go into an audit. And then I have to be in quarantine for two weeks after. It's not .feasible. And there are a lot of states like that where we have personnel that need to be able to audit and they can't."

Bettina Kaplan
Right now, with COVID, places are clearly not open for outside auditors to come in, or they're putting limited time there. What a lot of companies are doing, and what I'm seeing, is they will offer out virtual audits, where you can call in on a web meeting, they will open up their communication systems, the QA person will be there, they'll call in their SMEs as needed, and they'll let you go through the normal keys, documentation, manufacturing, lab documentation. What a lot of places are doing is they're setting up packets of information, but some companies will also provide a video. For me, a video is very important to see the site if I've never seen it before. For a new site, I want to see what the site is like. I want to see the areas, but for a repeat audit, I may not need to see the visual; I just need to see the updated documentation and the ongoing work. It all depends on is it new? Is it a company that you're looking at, or just evaluate? Is it a routine audit?

I think that many companies are going through virtual audits because they don't know where the future could be. Some of the companies that are affected by on-site audits are now saying, "No, we'd rather a virtual audit, we don't want to be on-site, we see a lot of problems, and we don't want to take a chance." The other issue is going through an audit. If you're from a location like where I live, I'd have to be in quarantine for two weeks before I could go into an audit, and then I'd have to be in quarantine for two weeks after, it's not feasible. There are many states like that where we have personnel that need to do audits, and they can't. The virtual audits for the COVID time period are the best way to meet your compliance requirements. I heard that the FDA is also looking at virtual audits of some type to do inspections or virtual inspections. They also recommended in guidelines for PCPs that in order for some of the clinics

to be monitored, they're discussing visual meaning, or something like that, to evaluate looking at the documentation.

Ed Narke
Okay, you mentioned certain things like the visual and virtual videos, and I think I have a couple of questions around that. How do you prepare for a virtual audit? You know, the traditional audits are suspended. The pandemic is probably here for a while; virtual audits might no probably will be here to stay. Maybe that's where we were going anyway. Some things are mission-critical to the piece of drug development. Generally, how would you prepare for a virtual audit?

Bettina Kaplan
Again, depending on the type of audit, it all depends on how I prepare for it. I request specific items from every company, whether it's a virtual audit or an on-site on it. I'll ask for general documentation. I will look at some of that before I even go to the audit to know what to expect. Sometimes they will send you some of the key SOPs ahead of time, or they will share it just on their secure server. Some of the bigger companies and some other small companies don't want to share their documentation with you by email because of the obviously reasons that go without saying, or they don't like to share because they think you'll take their work and use it. Another way of preparing, as I said, is looking at the FDA website, looking at what their last inspection was like if they have not sent you their EIR. A lot of the time, I asked for their last EIR to get an idea of what is at the site. Also, when I look at the EIR, I have ideas of where their weaknesses are, where their strengths are. And that's where I can also pinpoint my audit. So, if the FDA has found things, I will look at those areas to see what they've done. The other area I look at is the current trends, where the FDA sees a lot of observations. Other deviations, which are always the main items that they have, in almost every inspection. There are certain key areas that you look at every time, but preparing is important, and knowing what you need at the site and what services you're receiving because you want to make sure you're covering all of that.

Ed Narke
Okay, and then you mentioned, states and localities are opening at different stages. Things change again, like weekly in some cases and geographically, as well. You mentioned the quarantine portion. Can you talk about some of the risks associated with not preparing or not having an audit?

Bettina Kaplan
Well, the big thing is, besides not having control over your site, it is a requirement, a compliance requirement. Since we've already been four months into this and have no idea when the end is in sight, is it a year from now, is it a year and a half? In a year and a half, a lot can go on with a supplier, and you need to know what's going on, you need to know that you have control over your supplier, that you know they're meeting the requirements and there aren't things falling through the cracks. COVID affects the suppliers as well. They don't have enough staff. They may not have enough qualified staff, and things start to fall through. I have seen several companies where the limits of deviations, planned deviations, and mistakes occur because they're limited with staff. It's even more important then.

Ed Narke
Okay, can you see any differences between a well-established facility that may have been audited and inspected versus a new facility, which is more high risk for the FDA?

Bettina Kaplan
I think that any site can have a problem. I believe, large sites and small, you still have to keep on top of them, and you have to know what's going on. Large companies can have problems just as easily, if not more, because it becomes more challenging, they're open for work because pharmaceutical companies are considered essential. If

one person gets sick, they can get the whole staff sick and have a critical problem. If a large company or entire organization or department is out, the work isn't getting done, or it's not coming down properly. People don't know; you don't have a lack of knowledge. A small company could have the same problem. Both large and small, I don't think there's a difference. I think it applies to both.

Ed Narke
All right. I'm not a quality assurance person; I asked a good number of questions, I still have some more, but I think Brian and Meranda may have a few additional ones here to take direction, maybe.

Brian Lihou
I've got one, Meranda, just quick. So, we talked about the virtual model. I know internally at DSI, we've got a procedure in place to handle that. How important are the expectations of a virtual audit? How important is flexibility? You may have, going into this, your expectations for what you will be provided. Then the supplier, who may still be making that transition and understanding of virtual audits, may not necessarily meet that. How important is that flexibility?

Bettina Kaplan
It's very important. You would need to be able to roll with what they throw. So, to roll with the punches and try to ask the question in another way so you could get that information. It's all about how you present your question. You can ask a question several ways and get different responses and information based on how you present it. If you ask for something, and they give you just the basic answer, or they don't give you the document, and you say, "well, we're working with this product, and we see something happening." I'm just throwing it out in the air, "no one understands how you would handle it, so could you please explain it to me, and if you have a procedure, go through it with me." It is just in the way you present it. Turning it around, being flexible, and not getting frustrated. One of the biggest things is you can't show them that you're upset. You need to just go with the flow. Just think in your head, "how else can I do this?" Once you start to get your hair up on your back, they may shut down, and that's what you have to watch. So, it's always important to roll with the punches, keep going, and think in your head, "All right, let me think of another way to get this information."

Brian Lihou
Yeah. Which is why I'm not in quality. I'm in production. So okay. [laughter]

Meranda Parascandola
Okay, I just had a question about the virtual audits. How accepting are the sites so far? Has there been a lot of communication saying, "look, we're not we're not ready for it?" Or, if they don't have an SLP in place, is it best to offer up our guidance on how to proceed with that? I assume or the smaller companies might be more accepting than larger ones. Do you have any insight into that?

> "How do you get the site that you're auditing to work with you? It's showing them that you're willing to work with them."

Bettina Kaplan
Now I see both large and small accepting the virtual audits. I've seen both. It is probably easier for a larger company to do a virtual audit than for a smaller one. With audits, as we all know, if you're in a small company, you're engaged in a big majority of the site. Whereas in a larger company, they have certain people, and they have people that handle the audits all the time, but for them, it's easier, it's routine, they have a process in place. Smaller companies, as they grow, may have had many audits; if they do, they can attest to it. So, you know, it may be new to them, and you just walk them through it. You say, "This is what our expectations are for the virtual audit," and if they've asked you any questions, you'll work with

them to make it easier and to make it work with their schedule. Again, you say how do you get the site that you're auditing to work with you? It's showing them that you're willing to work with them.

Meranda Parascandola
I sometimes know audits to put on the schedule are a lot longer in person because they have to arrange everybody being there and making sure your time slots are there and the appropriate people on their side. Do you think it would be a quicker process now that it's virtual that you don't have to turn around?

Bettina Kaplan
You still have those same people that have to be on the virtual audit, even though it's not on site. Could it be a little easier? Possibly, because you can work around the schedule maybe a little better, and they don't have to be there at a specific time, they could perhaps come later. That might be the only thing, maybe a little more flexible.

Ed Narke
That sounds like an advantage, though, right? You would have a virtual audit so you can have SMEs from multiple sites or wherever participating online, real-time during a tour versus maybe 5 to 10 years ago when that was impossible.

Bettina Kaplan
Well, there's a lot of benefits to having virtual audits. From the other side of someone who we are providing a virtual audit to, there's a cost-saving on airfare, hotels, and on travel time that we're doing it just from our home, for the key audit time, and that you're not paying for multiple people to travel. Everybody is just joining Zoom, and you're paying for the time provided for the audit and the write-up. There are economic positives to this, as well that you can look at and say, "Well, maybe this isn't a bad idea," but I don't think you can ever get rid of on-site audits permanently. I believe that virtual audits may be something that will stay, and people will use them in the interim, but you need to see the site every so often because things change, and you want to make sure you know what's going on at that site, or if it's a new site, you need to see it. Virtual audits, I think, are here to stay.

Ed Narke
As we talked about traditional on-site, and now we've kind of touched a little bit on virtual audits and how they're evolving and may be part of the future, especially for companies with budget and resource constraints. We talked about a few things, the benefits, the advantages and some of the disadvantages. Are there audit alternatives other than those two?

"A paper audit is never as effective as a virtual or on-site audit. A paper audit a lot of times can be used in conjunction with the on-site or virtual audit."

Bettina Kaplan
A paper audit is never as effective as a virtual or on-site audit. A paper audit, a lot of times, can be used in conjunction with the on-site or virtual audit; it will help you prepare for a virtual audit by having them fill that out, the same thing for an on-site audit. I like to have, especially a new site or a repeat that you haven't been on-site in a while, having them fill out what is currently their practices. With paper audits, the only companies that I see paper audits being used routinely is for an excipient or packaging component that's not a primary packaging component, like corrugated or sugar. You know it depends on if it is the critical excipient or critical material, but I think on-site and virtual are not going to go away; those are going to be the primary way to do an audit.

Ed Narke

So, what we learned today from Bettina, virtual audits during a pandemic can sure a continuous supply of much-needed drugs, not just in the US but around the world. One of the advantages is to have SMEs from multiple sites they can participate in this audit on answering questions and getting to know the CMOS. One disadvantage, obviously pointed out by Bettina, is the inability to read body language and sometimes get underneath the cover. Sometimes it's hard to get a great read on the status of an audit when you're not there. So, we'll work on this. That said, thanks again for joining us on CMC Live. We hope to have you back to talk about more QA issues in the future. So, the real question, are you a Mets fan? Or did Bob just say that you're a Mets fan?

Bettina Kaplan
Thank you, Ed; I am a Yankees fan. Yankees all the way.

Brian Lihou
I could've called that one.

Ed Narke
Well, I have a question. What are your thoughts on the Mets this year? 2020, this summer, if we even get through the season? Any thoughts on that one? Are we going to go Yankees or Mets? If you had one pick for the World Series this year?

Bettina Kaplan
I want the Yankees all the time. Although, I will tell you that when I was pregnant, I walked out with the Minnesota Twins shirt. Because I have twins.

Ed Narke
That's cool. Well, we did go on that spring training game.

Bettina Kaplan
We did, and you know what, Ed, I enjoyed it.

Ed Narke
Yeah, that was about the second to the last spring training game. Everything got shut down the next day, and we all became self-quarantined and locked down.

Bettina Kaplan
Now COVID is down here.

Ed Narke
I went to spring training this year in early March, about six games, and that was where you could start to feel what was going on in the world because I do some investing as well, I follow some news on the trends and travel and the industry and I heard about this Corona something, and I was thinking, “oh the corona beer, right.” On the last two days of the trip, I think it was like the last flight back, March 10th. I remember because it was my son's (Kellen) birthday, and by the time I got home, I was like, "Alright, no more restaurants", didn’t realize Schools would become virtual as well. We thought it was going to last two to three weeks. The rest is history.

As we touched on, some of these things breed, you know, the future evolution of our industry. You know, we all know about Zoom calls now. Now we wouldn't be doing this if we didn't kind of get pushed forward pretty quickly. I think at the end of the day, it's just a lot of benefits and positives. I think a lot of small biotechs can be served by this virtual audit, not a lot of them have the money and the resources to spend, but if this creates just

another little bridge to keep them compliant, keep issues from preventing any delays, or any issues overall, it's certainly a good thing. Once again, Bettina Kaplan, thank you, and we look forward to talking with you soon.

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