

Filter Validation & How It Impacts Getting Your Product to Market

Episode 22



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Shelli Connelly
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A DS Inpharmatics Production

Ed Narke

Hello everyone, and welcome to another episode of CMC Live. A vital part of the clinical trial, or putting a marketing application in CMC, chemistry manufacturing, and controls. Once again, our goal is to help you reach your next milestone by providing scientific and regulatory expertise in all areas of CMC development. We'd like to help ensure your program progresses as scheduled. You need some sharp specialized guidance and support during your development program.

Today, of course, is National Chocolate Mint Day, which the US National Confectioners Association recognizes. National Chocolate Day is observed annually across the nation on February 19th, and I bet you didn't know that. It's set aside basically for all the chocolate mint lovers to eat their favorite treats all day long,

“Filter validation provides documented evidence of the functionality of the filter under the same condition in which it will be used during the pharmaceutical manufacturing process.”

Today we're chatting with Shelli Connelly, live and virtual, from out in the Wolverine state of Michigan. Shelli has been involved with us here for a bit involved previously in her work experiences with tech transfers of sterile parental products, including working with supporting departments, companies, and customer representatives. She's facilitated and finalized project timelines, scale-up, bulk compounding, release testing and has been involved with quite a bit.

Before we go on to that, though, as I mentioned about CMC, the process of bringing a new product to market is long, complex, and it's often expensive with essential decisions that you must make at every stage. It becomes more of a challenge when you're developing a sterile product, of course. The sterilization method is a critical consideration in drug development, and it may be done by stroke filtration followed by aseptic filling. Although the decision to incorporate filtration here hinges in part on performing validation work to ensure that the filter used to eliminate any microorganisms is the right one. Performance is key. Ideally, filter validation would be carried out in the very early stages of production.

However, that's not always the case. If so, it's usually in conjunction with other validation activities, like media files, to guarantee the sterility of the final product. Deciding when to carry out filter validation work requires bouncing a range of practical considerations. As you guys know, agencies like the FDA or European Union provide guidance documents and set regulations that dictate the requirements. Other organizations out there include Parenteral Drug Association, PDA, for example. They developed technical bulletins, which you should check out; they're very enlightening. They also provide information on the topic, one of the fundamental

activities documenting the production process that complies with necessary regulations. It's critical to show that the filtration process will consistently result in a product that meets all the required quality standards and characteristics. Filter validation provides documented evidence of the filter's functionality under the same conditions you'll use during the pharmaceutical manufacturing process.

We're excited to talk with Shelli today here. Shelli will discuss some of the elements to filter validation, including integrity testing, fit for use sterilization, bacterial retention, extractable, etc. She'll possibly be giving some of her real-life experiences. I want to throw it over to my trustworthy co-host today, Brian, Brian Lihou, to provide a further introduction. Brian is our local product expert, as well as a few other things.

I look forward to this discussion here, it's out of my background and technical area of expertise, but I hope that you'll enjoy it as well.

Brian Lihou

We've got with us today, Shelli Connelly, here at CMC Live. Meranda and I were fortunate enough to get Shelli, a Senior Drug Product Consultant here at DSI with a host of experience in sterile injectables. What we want to talk about today is filtration. How do we select a filter? How do you qualify for a filter? How do you validate a filter? We get many questions, and we thought it'd be good if we could kind of break down the fundamental components. So why don't we start with Shelli? Why don't you introduce yourself? Tell us a bit about yourself.

Shelli Connelly

Sure. Good morning. My name is Shelli Connelly. My background consists of almost 25 years of a sterile drug product. I have done everything from clinical-toxicity-lots through registration, validation, and commercial scale-up. Filter validation is always a fun and hot topic regarding filings and/or any type of changes that may occur over a product's lifecycle, like increasing batch size or changes of API or excipients, or even process. Those all need to be considered when looking at filter validation.

Brian Lihou

Why don't we start from the beginning? Let's say that we have a process that is a pilot-scale batch, and it requires filtration. How do you go about selecting a filter? Not all filters are the same, and perhaps you could talk a bit about how they're not the same and how you select a filter.

Shelli Connelly

I think it's important for us to know about your product in general. What is your formulation? Is it water-based? Is it oil-based? Most injectable products are water-based, from what I've seen, and normally two filter membranes are the most common. It's the PVDF and the mix esters of cellulose. Those are the two most common sterile filters I think I've seen over the last 25 years. But if you have a product that may be ethyl alcohol or have a different type of the main vehicle, you may need some kind of nylon filter or something like that. So, I think knowing what your product formulation is and understanding that more so from a chemical side or the laboratory side. I think you start with that and then perform some compatibility studies upfront. They have those small 47-millimeter disc filters that you can purchase, and a lot of the analytical people know to do these quick studies, and you do them over time to see if a filter would be compatible with the product and start there.

Brian Lihou

What are typically failure modes and filtration? As you eliminate the prospects for a filter, what do you usually see in terms of failures?

Shelli Connelly

I think from a failure mode perspective, I've seen companies not know enough about their product in general and pick the wrong filter. So, I think, starting still upfront, even before you get started making batches, is if you're unsure you don't have enough experience with that, I think reaching out to the filter vendors like Millipore, Sartorius, Paul, The Big Three, and get with them to do a filterability test upfront. What they can do is they can pick out four or five of their filters, looking at what your product contains, and do a quick down and dirty study, and kind of lead you in the direction of where you need to go from a filter perspective, so that you choose the right one before you even start.

Brian Lihou

Okay, so basically rely on their protocols, and they'll walk you through the process?

Shelli Connelly

I think, especially if you're a young company and don't have experience doing filter validation, I think that's a great start. Many of them will do filter feasibility studies, like filterability studies, even for low or no upfront cost. They do this because they know once they give you a filter, you're going to buy it from them. So, it's a great thing that they do for you, and I highly recommend reaching out to the filter vendors. They're the best support, especially with this.

"I highly recommend reaching out to the filter vendors. They're your best support, especially with this process."

Brian Lihou

Not to get too far ahead, but I would imagine all that information you get back from the vendor falls into the product's development history. So, you would ultimately need that.

Shelli Connelly

Correct, you can absolutely utilize that. Again, I don't think it would necessarily be needed for a filing. Still, it would be necessary for the product development folks who may need a bit of back history about what was done with those filters. It will help the process development group proceed and move the product through to commercial.

Brian Lihou

Now we talked about material compatibility. How about sizing the filter? Does it matter what size because they've got these great little disc filters? They're cheap, and I could run all day on them.

Shelli Connelly

Of course, size is very important. Size is interesting how it has evolved since I started. Back in the day, excipients and things were a lot dirtier than they are today; things are a lot cleaner. So, in that sense, yes, there are normally definitely different filter sizes, and it's mainly related to, what's your batch size and what kind of bio load are you putting into it during your formulation process? Looking at your overall product formulation? Is it something that's a little more viscous? Is it going to clog your filter? You need to know about your overall formulation and look at those things.

Brian Lihou

Is it a recirculation study? Let's say, for example, we're moving from a small two head filter to a larger eight head, and it's going to be running eight hours, and you're pushing more volume through those filters. How do you establish that surface area? How do you determine that?

Shelli Connelly

Some can also relate back to those filterability studies with the filter vendors that you initially do. When they start with a drug process, most people look at normally less than 100 liters, knowing that your commercial batch size could be 1500 liters. Then the question also comes down to are you doing redundant filtration? Are you utilizing two filters? Are you utilizing one? I think kind of understanding your product and the filter vendor still can help with that. I can't say in my history, I don't think I've ever gone really over a 10 inch, there may be a product that has gone 20 or 30 inches, but it's a unique product. The majority of injectable sterile products are going to be 10 inches or smaller. If you have a 100- or 200-liter batch, normally you are using a four-inch or six-inch filter, and I'm mainly focusing on water products here, but oil-based products may be a little different in that sense, which gives you more information.

Brian Lihou

Filters have evolved. When I first started, everything was the plate and frame filters with all the lovely ways they can leak. Now it seems to be a lot more. They're pre-sterilized, and they're packaged. Do you get many calls for the old stuff? Or is it pretty much single-use disposable, no housings, things like that?

“A Bubble Point test is related to the micron-size of your filter, meaning if you have a 0.2 or a 0.45, those bubble points are gonna be different.”

Shelli Connelly

I think that the push in the industry is definitely to go more towards the disposable route. Some products can't do that; they may need heat during filtration and need a jacketed filter housing. So, in those instances, you can't really go disposable. However, overall, I would say for sure, the industry has moved more towards disposables. You will not have filter failures and setup problems. I mean, they come to you ready to use, and they are very robust. The disposable filters are very robust.

Brian Lihou

Do you hear that? All your development people out there, think about the end-user. Think about those of us on the line that are assembling those filters, filter assemblies, pressure testing, and everything that comes with it. It's a lot easier to unwrap them, put them in your autoclave load, and be done with it.

Shelli Connelly

The same would go for vent filters on tanks. I know, a previous place I worked at, there was a big push to get rid of the stainless-steel housings because they were having issues with bleed valve failures. As soon as we switched over to disposables, we did not have that issue, and it all the way around saves reprocessing, time, money, resources, all of that.

Brian Lihou

Yeah, you've got the sealing surface of that gasket will get nicked, and it may not seal. Then you've got people taking wrenches to the clamps and trying to torque them down. Love them. So yeah, it just takes the guesswork out of it. So okay, now we've selected our filter. Do you have to qualify a filter before you validate it? Or how is that done?

Shelli Connelly

So normally, if you're utilizing a sterilizing filter at the 0.2 microns, you must run it through some type of sterilization process, either autoclave, gamma, or radiation. It just depends on the facility, where you're at. Suppose you're at a contract facility, normally you have to go with what the facility has in place and/or uses regularly.

Brian Lihou

Often, the CMOS will buy in bulk; you'll get a better deal passed on to you for the filters because of the sheer number they're buying. Now, when you talk about things like filter validation, at what phase in a program do you need to validate or filtration because, in phase two, you're going into a human? When do you really need to have that line in the sand in terms of sterility assurance and validation?

Shelli Connelly

Sure, for sure, filter validation needs to be done either before or in conjunction with registration batches. You will need the filter validation for the filing. It is a requirement. So that's going to have to be done before then. For commercial products, if you change the batch size and go bigger, or do any other type of different change, or your filter parameters will change in any way, you will have to go back and revalidate your commercial process.

Brian Lihou

Okay. When I first started, which was a while ago, pre-use integrity testing was a business decision. Well, we did it because we wanted to ensure the filter, and sometimes, as you mentioned before, it's the assembly of the housing and all the time things that could influence it. But we weren't pre-use testing all the time. Now, it seems that the sites that I've visited appear to be more than the norm. So, with pre-use testing, how do you address that? How have you seen it?

Shelli Connelly

Actually, I have seen it both ways. In my professional opinion, I don't think it's necessary. Many people are doing it if they have super expensive products, which I completely understand because you don't want to be throwing your products out if you have a failure on your filter. I have seen two, only two, true filter failures in my years, especially on the disposable housing. They're very rare. All filters made by the filter manufacturers are integrity tested. Each filter is integrity tested to show that it meets its minimum bubble point requirements based on what the vendor has provided. So, in that instance, I mean, you already have the assurance that it is a good filter.

Now I know there was talk about shipping and this and that, but I just haven't seen any issues with the shipment and or gamma radiation, really causing any pre-use filter failures. I think it comes down to if you're using a CMO or just having new products come into your facility that are your own. It's probably legacy as to whatever it is that company has been doing. I think it's kind of on the fence, depending. It just depends, and if you're going over to the EU, they require you to do, I think, a pre-use filter integrity test. Though, I hear you may be able to risk that mitigation out with documentation as well and maybe skip that.

Brian Lihou

Qualify the vendor, yeah. You mentioned something that I'm not sure our listeners fully understand; some do. You said bubble points. Now the bubble point references, you go back to the days of yore when you were looking for bubbles, but what is the bubble point test? What does it do?

“Most people when you start with a drug process you’re looking less than a hundred liters, knowing that your commercial batch size could actually be 1500 liters. And then the question comes down to are you doing redundant filtration, are you utilizing two filters, are you utilizing one? To understand your product, I think the filter vendor can definitely still help with that.”

Shelli Connolly

So, a bubble point test is related to the micron size of your filter, meaning if you have a 0.2 or 0.45, those bubble points are going to be different. What ends up happening is you get your filter membrane, and all you're really doing is put pressure on the upstream side of the filter to allow air to get through the pores. The bubble point value is in relation to the micron size of the filter. For the 0.2micron filters, it's normally around 50 psi or 48 psi. So, what ends up happening is once you start the test, the pressure slowly increases up to that minimum point. What will happen is bubbles will start going through the pore size, hopefully above 50; that's the goal. Then you have a passing test. It has everything to do with air pressure and allowing that pressure to go through the pore size of the filter.

“I think utilizing your filter validation in conjunction with your media fill program – whatever that may be – they have to be synced and in alignment.”

Brian Lihou

Okay. When I first started doing this, we didn't have machines, and we didn't have the Millipore integrity testers and things like that. All the major vendors have them, but now they do. I think one thing to note, for those of you working with CMOS and doing a lot release, pay attention to the calibration data of the tester. The fact that the tester was validated, especially sites that use multiple testers and push them around in different areas because it could really impact your filter values, which could ultimately be the disposition of your material. I think that's an important thing to note when you talk about integrity testing,

Shelli Connolly

I would agree.

Brian Lihou

Okay, we talked about how we selected, so you look at the composition of your product, the compatibility of the material of the membrane itself, you look at the surface area of the membrane, in terms of the volumes you're pushing through. Then we talked about what integrity testing actually is; these are all good things to clarify. Now you get into filter validation. Now, much like the compatibility, a lot of vendors will take care of that for you and put together a protocol. You review the protocol, but what exactly goes into filter validation?

Shelli Connolly

Initially, what ends up happening is that each filter validation vendor has an information sheet on your product that you must fill out, meaning they want to know certain parameters. How is your filter-sterilized? What is your batch size? What is your flow rate per minute of the solution? Is it cold? Is it room temp? How long are you doing an intermittent filtration where you filter for a little while, then it sits. Or are you doing continual filtration from like a tank to a tank or bag to bag? All those things play a role in your very first step of filter validation. You need to know all those things for them to perform the validation successfully.

One word of caution I will say on that is if you are uncertain of what your batch sizes are going to be from a commercial standpoint, and let's say you're thinking, it's only going to be to 200 liters, and then a year from now, all of a sudden, 'Oh, my gosh, it's a blockbuster product.' We're going to scale up to 400, and you will have to repeat your filter validation a year from now if you don't do more of a worst-case. So, when filling out those filter validation forms, I highly recommend doing a worst-case scenario, which means, how long is your intermittent filtration? If you think it will be 24 hours, you really should be validating 36 or 48 hours. If your batch size is 200, make it 300, give yourself a little wiggle room, don't validate your process at a set batch size, give a range like 200-300L. or you're going to find yourself repeating all of this and filter validation is not cheap.

Brian Lihou

Well, that's something else to consider. I know. I worked at a site where our one commercial fill line was it was problematic. It was an old design; it was prone to failures. We got very good at making repairs in an aseptic environment, but what it would do is it would draw out your processing time. So, our rate limiter became our filter validation, and we would have to throw away or hold the product back out of the suite to re-filter and find time in the schedule to finish it. So really, having a proper understanding of everything that makes up your aseptic processing suite and making sure that time covers excursions because you will have them.

Shelli Connelly

Absolutely yes. You don't want to plan for them, but you need to because it does happen. It just happens.

Brian Lihou

Yeah. Can you do filter validation in the house? Or do you really have to rely on your vendor?

Shelli Connelly

I don't know anybody that is doing it in-house. I think everybody is using vendors because there are so many other things that go on from a sterile drug product perspective. It is just one thing that I think almost everybody is leaving with the vendors and/or laboratories that do some of the work. I don't know of anybody that is doing it in-house. There's, you know, a lot of different filter validation documents that are needed to support your filing.

Brian Lihou

Okay, that's a good point, and it's highly scrutinized. I found that over the years, inspectors tend to gravitate things they're comfortable in now, sterile filtration has been around forever, and aseptic processing, so you get a lot of questions. So, here's one, I'll throw a curveball. If you don't have a term of the sterilized product and your media challenges, how do you use a filter and immediate challenge? Because, I mean, you start with a known bioburden, let's say about two filters in series, you put actual filters in when you're trying to quantify the product pathway, and you're going from a tank to a filling reservoir on a machine? If you're running it through sterile filters, does that negate what you're trying to prove upstream of the product pathway? So, how do you use filters and immediate simulation?

“Normally if you’re utilizing a sterilizing filter, you definitely have to run it through some type of sterilization process.”

Shelli Connelly

So, I think, when looking at your overall process times for a product, I think utilizing your filter validation, in conjunction with your media fill program, whatever that may be, they have to be synced; they have to be in alignment. Not only should you be looking at your workspace parameters from a filter validation perspective, but also those parameters that you pick must match, or media could exceed them, which is fine. They either need to match or exceed from an aseptic media perspective because they work together. There are two different aspects of sterility per say, they feed into your final product, but they must be together. From a selection of a filter, I think you need to choose the right membrane from a media perspective. You can't use a nylon filter, and I'm sorry it doesn't mesh well with media; it'll clog. You need to make sure you're picking one that's water-based but really focus on whatever type of connections you're using for the product. You need to ensure your connections for your media are the same because that's really what you're looking for. Maybe not necessarily the membrane, in general, from a media perspective.

Brian Lihou

It's really contact with the media and all the key aseptic connections along the route, right?

Shelli Connelly

Correct.

Brian Lihou

Okay, one last question. I have completed my filter validation. When I look at compiling my filing, I'm going for my NDA, my BLA. How much of my filter validation do I put in? I know it is a regulatory question, but I know you've been very involved in all of that. Did you hold it back and wait upon request? What's your philosophy in terms of what's included?

Shelli Connelly

I've seen it many ways, but more recently, I think I'd say the top four filter validations that are being done are bacterial retention, compatibility, product bubble point, and then they also want extractables. I have seen companies submit all four but then not necessarily make a product bubble point for their product down the road. Product bubble point is interesting because I know there was a big push years ago to move towards product bubble point. But a program like that, especially if you are working with some type of CMO, you would need a person just to man it, mainly because if there are any, again, API changes or you change manufacturers, you must go back and repeat your product bubble point.

So, I think there are almost recommendations as well to keep somebody to oversee your product bubble point throughout the year and kind of come up with an overall summary to ensure you do not see the drift, or you're having filter failures because your product bubble point values, you know, may have shifted because of maybe something you're unaware of. Maybe the vendor, API manufacturer, made a change, and you didn't think that would impact your product bubble point, and now it is. So, I've seen the product bubble point completed and then filed, but then not necessarily even utilize the information. I think, especially from an FDA perspective, they're looking for all four, even if you don't use it, which is interesting to me, but that's just kind of what I've seen the most, as people are doing all of those and submitting all of them.

Brian Lihou

Okay. You mentioned something, though, early in your explanation, and you mentioned the term extractable. So, for the benefit of the folks listening in, what exactly are extractables?

Shelli Connelly

From an extractable filter perspective, the extractable has been going on for quite a bit. From an extractable standpoint, most of the vendors use almost like a worst-case solvent stream where you're at low and high pH's, and they're using solvents to ensure that nothing is getting extracted off the filter and into your product. That is really what you're looking for there. So, in that sense, that testing has been going on for quite a long time. I want to say I don't think I've seen any products where actual extractable testing had to be done on the product. Since a lot of the filter vendors have done these model solvent stream worst-case scenarios so that your product normally falls into that grouping. It's easy for them because they have all the data, they can provide you from an extractable standpoint based on the worst-case scenario they're utilizing during the testing.

Brian Lihou

Okay, so as we're winding up, is there any bit of advice you would give, say, a sponsor who just got out of the pilot plant looking to get into clinical production? What sort of considerations would you recommend they do in terms of filtration?

Shelli Connelly

I think the biggest one is ensuring that the product is compatible with the filter and not having any issues in doing some small lab scale studies and taking even a liter or two and running them through those small disc filters. So, it will tell you quite a bit in doing that, I would say.

Brian Lihou

That's good, words to live by, because every time I think that the box check common sense is known by everybody, we come across a situation where it's new and exciting, and you must explain it. I want to thank you for your time. This has been most informative. Again, we have a lot of inquiries from various companies talking about culture compatibility, culture validation. Do I really need it? I think this really explains a lot of the basic terms and the concepts and timing behind why you do what you do. Thank you very much, and we appreciate the time.

Shelli Connelly

Yep, thank you!

Ed Narke

Thank you again, Shelli. To recap some key questions and discussions, knowing a bit about your product is important. That sounds very generic, but it's true. For example, if it was water-based, we talked about if there's a different solvent, it makes a big difference for the materials you're using. I need to think about that, you know, how compatibility studies, for example, play a role from the beginning. You look at the compatibility, of course. We discussed some of the things around failure modes; it was interesting. What do you do if you pick the wrong filter? We talked about dialogues, interactions with some of the larger filter vendors and providers. This is a key factor and is very important, especially if you're a young company that may not have engaged in this so much or has that much deep experience. How filter vendors are talking to them and how they work and operate, they're the best resources, and it's important to speak with the same language and speak to them. As someone mentioned, size is definitely important.

Successful filter validation requires a partner, obviously with experience and properly evaluating and documenting such elements of filter validation. Failing at any of the steps listed above where we talked about during the podcast, can lead to costly delays in getting your product to market. So, whether you're an early-stage company or looking for a partner, take your sterile product into GMP manufacturing, contact us to discuss some options, and we can help with that. Again, you can benefit from our experienced team here.

On the next podcast, we'll be speaking with Dr. James Mencil. Jim's back once again, of course. He was our first guest on our first two podcasts this season, and I encourage you all to catch them. Once again, very great information. He goes over process validation a bit, as well, and he'll get into that a little deeper on the next podcast. So, join us next time, and I thank you again.

FDA CMC regulations and guidance are simplified through examination, real-life experiences, and risk-based advice. This podcast hopes to educate sponsors and individuals on agency-related regulatory CMC matters. We will focus on the critical CMC issues and build programs that enhance drug development. CMC topics will include Regulatory Starting Materials, API and Drug Product Process, Formulation Development, Supply Chains, Analytical Controls. Advocating and interpreting CMC Strategy, directing CMC Operations and Quality Assurance oversight in conjunction with developing CMC submission content that represents the best interests of emerging biotech. NOT INTENDED TO BE PRESCRIPTIVE ADVICE BUT RATHER AN INTERPRETATION THAT IS RIGHT FOR YOU. Since 2007 we have provided our partners with innovative strategies and exceptional advice intended to enhance program development, product approval, and marketing presence.