Regulatory Odd Couple

Episode 21

Meranda Parascandola
Hello, and welcome back to CMC live. My name is Meranda, and I am joined by Ed Narke today, today's podcast, I wanted to have to pick Ed's brain about the regulatory Odd Couple blog series we have on our website. It is a seven-part series with two primer blogs. And there is a chock full of information for regulatory submissionin those. So today, I wanted to bring Ed on and ask him where he came up with the idea for the regulatory Odd Couple, which is kind of timely having Valentine's Day just right around the corner. So, Ed, welcome to CMC live,please tell us a little bit more about the regulatory Odd Couple where it came from. And also, I'd love to ask you some questions about regulatory offering.

> "If anyone's listening and not familiar with the drug development process, the one area that's most important is the FDA guidance."

Ed Narke
Welcome, everyone to CMC live. This is our special Valentine's Day edition. Hopefully, you'll be doing something interesting with friends or a partner this weekend. So hello, Meranda, how are you?

Meranda Parascandola
Yeah, I'm doing well. How about yourself?

Ed Narke
I'm doing great. Do you guys celebrate Valentine's Day?

Meranda Parascandola
Yeah, we love Hallmark holidays, it's really a great way to connect and know that we love each other on a specific day of the year.

Ed Narke
Great. Yeah, so it's getting less and less celebrated for the Narke family here for last couple years with the kids, you know, they now I guess we have to sort of support them with their friends and loved ones too. So, but we havewe have a couple of rituals. So anyway, it is the Valentine's Day 2021 edition. And I namely aptly named this one,the odd couple. He's never developed a regulatory submission, and she's never submitted one. So why are we doing this? And what are we talking about here? So, you ever wonder why you're spending the time and effort on generating this regulatory content that we all know that that's required? Right requested by the reviewers. The FDA ama question is like, how many times or how often have you wondered whether the reviewer realizes the impact of what they're asking for, you know, they're not familiar with your program, your process your methods, you know, their checkbox going down the list, of course, you know, it's very, very important some of the requirements. So, you know, we will go through this here in our in our podcast today, we also have links to

some previous articles, written blogs, and etc., evaluating some of the more common issues that arise when sponsors prepare their common technical document, the module three in the quality sections, and maybe talk about some examples of some of the things that come up pretty frequently that we've seen, you know, continue to see.

But I guess first off Meranda, the CT, Module Three, for those that aren't familiar with it, right? It's the module three, for example, specifically, it's detailed description of the CMC chemistry, manufacturing, and controls information associated with that drug substance and drug product and your substance could be well characterized, synthetic molecule new chemical entity or you know, something that's been around for a while, or it could be a biological program or product that's generated from fermentation process. No matter what it is, it's the active ingredient basically, that goes into the product and you know, it's creates the efficacy and there's things like that does the job so that's formulated into a product, some sort of formulation, oral, solid, intravenous checkable, etc.

So, but anyway, all this information, right, provides assurances that the compound meets the requisite technical and quality elements to compliance pieces, right. And that all builds over the course of clinical development into a marketing application, you know, that's submitted for commercialization approval so you can sell it usually that's probably where you're going with this right well, and there's a different markets. You know, there's different reasons to you know, smaller markets, there's still sort of an audience out there, patients and etc. So, but all the compliance pieces are relatively the same. You have your process information, you know, your characterization information, your specifications, which are which are your, your analytical methods and your specs. So, anyway, but we can refer back to that again, here, the but the, you know, the blogs if you want to go back to them, you know, provide an overview of the same information, what has to be prepared, sometimes when we go through the common technical document structure, essentially and tying it back into the odd couple, there's various and opinions on what you need to provide how you need to provide it, how much information how little information so, again, I worked with a lot of regulatory submission authors in my career and there's different policies, there's different thought processes. You know, my only word on that is, you know, do what makes you feel comfortable and entered into the risk that you're comfortable with. So, for example, I would say that, you know, you don't have to provide everything that seems to be, you know, some folks preference, sometimes that could lead to maybe just additional questions, you know, you're just kind of going too far, tell him a little bit too much of the side story, and then giving no information is probably not a good idea, either, only because it'll beg for questions, right, you're going to get additional questions. So somewhere in the middle, you know, sounds good. I think when I worked at larger pharma, and I was trained on this, you know, a little bit of information was not good, you know, somewhere in the middle, at least, as far as I recall, you know, you have a lot more information, especially big pharma, especially when you're generating lots of batches, lots, lots of data, you know,you can essentially hold a lot of information, and then you know, you're gonna know, get a feel sometimes where the questions could come based on your process, or, you know, the complexity of the program. And it's when you submit a marketing application, it's, it's probably a good thing to take that data that didn't submit, and then you know, kind of almost self answer questions that you can anticipate, you know, get that data, put a story together, and that, in essence, it's a little legwork. But you know, you'll have it ready when the questions come, or if they come. And, you know, you could, you could attack it that way. The challenge, I think, in our role here, Meranda is,you know, working with small biotechs, they don't normally generate a lot of data, for obvious reasons, it costs a lot of money, right, you have to pay CMOS, the contract manufacturers, a lot to make batches. So, you know, you really only kind of making and creating materials that you're going to use and then commercialize. And, you know, we've worked with companies often that are just three batches, that's going to be their clinical material, that's going to be their launch material. And they'll do studies and stability studies and validation with that. So, they may not, you know, have a full understanding of all the sweet spots of the process or where the edge of failure is, they may not have done all of the, you know, factorial design work or the design of experiments.

Usually, that happens for those who are pretty familiar with drug development that happens early on in the background, sometimes informally, scaling up processes. You know, if you're working in a process Development Lab, API scale up and product, the same thing, you need to do smaller studies, to kind of get an idea in a realm

where you're going to be and then you'll eventually scale that up. So sometimes you can leverage some of that lab work key lab work. Some of that's small scale production work, especially in cases where you're, you don't have enough stability and you want to support that or show you know that the product is stable. And a lot of that could be used, obviously in the clinical in the updated whenever we get new information or when things change. So why don't we get right into it, though? So constructing the module three a primer. So Meranda, do you have any questions?

Meranda Parascandola
Yeah. So where does somebody start when they are intending to file NDA or BLA? I think we come into it often when clients don't have a lot of data, or they generated the wrong data. So what would you suggest to emerging biotechs to look at, or think about first, before even getting to this point? They're gonna have to generate some data gonna have to author their marketing application, what should they review, it could be our blogs, or maybe some FDA resources that they may want to look at before they get too deep into it.

Ed Narke
Yes, certainly, if anyone's listening and not familiar with the drug development process, the one area, most important area is the FDA guidances, which are located on their website under the CMC area, and they cover small molecules and large a lot of those are referenced to the ICH International Conference harmonization, that's a body that harmonized a lot of the requirements for different regions to ensure that there's a consistency across the board. So usually, they're the be all end all they are on the ICH's website, you know, some of the things to consider early on are what you're going to need at the end. So, you're not going to necessarily generate them step by step, sometimes you'll actually even go to the agency and ask for some permission to not generate certain types of information because maybe it's not so relevant as part of the story. So I would say that the guidances and the requirements, the CFRs on the FDA website are kind of the be all you know, the guidances or guidances, but they're, you know, strongly recommended to follow especially when you get to the point of filing a submission, you know, usually you're not going to be given an opportunity to turn any information in or provide anything after, you know, unless it's missing and that could delay your application, your review period.

> "Characterization is, in my mind, one of the fundamentals of a product and a process and a program. If you don't know what you're dealing with to start, it's hard to catalog it, make it consistently and answer questions about it."

So, one of the other things to think about Meranda though, is and especially in our line of work here is who's generating the information for example, you know, traditional large companies may have facilities that headquarters somewhere but facilities that they own and operate you know, what you'll find in a lot of small emerging biotechs is they are a shell they have a you know, usually a management team, usually they're virtual, you know, they may have some medicinal chemistry or research labs, but they're not doing most of the testing or the process or not creating the materials, they're not doing, they're not operating under the QA that's, that's usually done by a third party, a CMO. And as far as, as far as that goes, the challenge there is there's opportunity to generate the right information, but it has to be managed properly. So the CMOS obviously have their business model is to create material for a certain price, in a certain timeframe to make sure that they have capacity to do that fill the capacity, and then they release materials to a sort of a legitimate specification to prove that they're making it consistently each and every time. So just to throw in here, the specification, you know, one of the main things is you have to make sure the materials are consistently made exactly the same, most, for the most part, they are the same as some of the other ones, you have to run additional toxicology and safety studies and stuff like that. So, gets into a much more complex discussion, if you're talking with biologics. So you know, you're going to be relying on your, your vendor,

let's say, to generate this information. So, if you're not looking after them, you know, you're not kind of piecing, you know, puzzle pieces on the table, right? If you're not looking at where things come in, you know, when they're needed, timing wise and stuff like that, you may run into some problems

later on, when you're heading into phase three, and you're looking at filing a marketing application, because you may find that at that point, you're missing some key pieces, maybe that you weren't familiar with. So any you know, anyone that's kind of putting an NDA together from the beginning, it's always good to have like a blueprint, you know, map, basically, to see where things are coming in. Sometimes data comes in the very last minute, you know, sometimes the last day, actually, so you know, you want to leave placeholders. If you're a regulatory person, and a small company, you know, you want to make sure that there's awareness of what's going to be your bottleneck, etc. So

Meranda Parascandola
That's actually a good lead into the next part of it. I was doing some submissions for a company, and we were always waiting on the quality overall summary, is it advised to wait to build the quality overall summary, or build it as you're doing your sections? Or explain a little bit more about what that is? If people don't know,

Ed Narke
Yes, this is another one of those Odd Couple situations. You know, like he says this, she says that they're not in agreement, the quality overall summary. Again, just for those who don't know, are not so familiar with it, it's sort of a high-end summary, you know, basically a quick synopsis of your, your program that goes into module two. But um, you know, it's, again, arbitrary, you know, you can wait till the very end, if it's a straightforward program, summarize things, put it in there, you know, I myself was taught to do it a little bit differently, you know, that's the cookie cutter model, you know, you wait till the end, nothing changes at the end, you put it together, yeah, you basically just put a snapshot redact certain things, certain things aren't necessarily necessary in this QOS. But I look at it a little bit different, I guess, from my trainers, or my mentors and teachers out there from back in the day, but I look at it as it's a good place to explain the things that are missing or not necessary. And then why certain guidelines were not followed. So that if you use that as a rule of thumb, you know, you, you probably could start to develop that story as you go along. As you have FDA meetings and the phase two meeting, for example, in Q1, you know, there's binding agreement that you don't need to do certain things, that's maybe where you cite your discussion, your compromise there with the agency in there, you know, to kind of remind them, and maybe relate back to where that dialogue and correspondence was documented. Also, for example, there's certain things you're not going to do with certain types of drug formulations. Certain types of API's might be obvious to reviewers. But you know, maybe that's maybe where you explain that sometimes you'remissing data, and you just don't have it, you're not going to have it a lot of times programs are put on hold or shelfed for a while, for reasons such as running out of money, resources, you know, maybe there's just too many products in the pipelines, some things are put on hold, and then they may license the product to a different company, a large company, maybe you're small, and you're not going to have some of that back information, that inherent information, you may not be able to go generate it. So that's where I think some of that missing pieces can be explained, you know, scientifically, of course, you know, you just can't say that you don't have the data, right. So and then, and there's no need to kind of pick it up here. There's no need to submit irrelevant information in there, redundant information, unorganized information. So again, just my opinion, you know, you as with everything, you want to start somewhere, somewhere, if you have a goal in mind where you want to be, even if it's just creating shell for the quality of real summary, putting in place markers, where you know, you maynot ever generate that information, you may essentially formulate into your questions, you know, for an FDA meeting or EMA meeting, you know, and that could be the basis for your briefing book, essentially. So,

Meranda Parascandola
There's a lot of sections that go into a filing, do people particularly start at a certain section or does it depend on as data comes in where they want to start? So, if somebody was building a marketing application, where would they start? Do they just start at S1 or P1, is there any guidance to that or just depend on the author,

Ed Narke

I think it depends on the state of your program where you're at. So if you don't have a thorough process that's established or scaled, you're gonna have limited information, you know, you may have some batch records and some slight early development reports on the process, but those things would probably have to be increased or some more data, so you're going to have to work on those sections.

Certain information, like the nomenclature, the molecular structure, the formula and molecular weight, those are things that won't change, once you identify and characterize your product, your API, you know, these are things that that are static, they're not going to change. So, these are also things that are in your IND, you know, these are requirements for your IND. Now, you will get other information characterization type of things, melting points, you know, hydric, hydrous, capacity type of information, partition coefficients, you know, if you have different types of some of that stuff comes in later, but you're gonna have a basis. So when you submit an IND, as we know, here, you're gonna have general information, you're gonna have basic information about the manufacturing process, you know, who makes it, how's the control to, again, like we said, consistently produce it, right, some characterization information, you know, the, the entity, the, the molecule is probably going to be elucidated by some sort of analytical technique, whether it's mass spec, or LCMS, or, you know, various types of different characterization. These are all in the guidances by the way. There's, you know, wish lists of things that you can use. And then some companies are using some new technologies to either save time or further characterize, to reduce question. And then you're also going to have some information early on in your IND around the potential impurities identified, you know, and you're going to characterize them and qualify them for safety as you go along, you're not going to know and

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you're, obviously your methods aren't going to be fully validated, you may not have all your methods in place. But to answer your question, I guess, to a lot of the information that you would kind of put into an IND that's required just to open an IND. And then as you evolve into phase two, and three, you'll have some of that stuff set, you know, you'll have that there. So, you can either expand on it, or some of the sections will almost kind of be complete, you know, from the from the IND stage container closure. For example, if you're using a vial, you have a cap, a seal decal, that type of glass, if there's no anticipated changes to a different delivery route, that would probably be sufficient. And that's that section is kind of almost done, you know, you're gonna have additional studies that you'll do on the container closure to ensure it's consistent, you know, it's consistently keeping the product under control. But those are things I think add, you can even add into other sections, but a lot of these sections have a basis, you're going to have specifications, your acceptance criteria, right, your methods and your spec, you're gonna have a baseline of methods, we covered that in a blog, I think was control of the drug substance, I think it was, but you know, kind of list outline, some of the kind of general specifications that are just always required are always required.

And then you're going to have you know, as youdevelop this more, you're going to want to find out, you know, control a little bit more scaling up, you may have to tighten it a little bit, you're gonna have a few additional methods, some of the methods that you use early on might be primitive TLC, and those type of things like that, as you get down the road, you know, sometimes it's more costly to develop a little bit more of a robust method. So, you'll do that later on, when some of the risk is based out, you know, when you have some efficacy data, you know, you're taking the product forward into a marketing application. But, you know, stability data as well, you know, you're going to be generating that over the course of your clinical development program, it just doesn't happen overnight. And lastly, on phase three, you'll generate that your formal stability studies at some point, and you know, that you can support your retest your expiry date there, that's going to become in you know, over whenever you take the readings every three months, or once a month depends on, you know, accelerated studies.

So, you'll have some information that just continues to strain in some information that just is dumped on you, you know, you, you engage a CMO to do a sort of a development study for certain reasons, a lot of those studies that are required information for the pharmaceutical development section, the drug product happen that way, you know, you'll put effort into studyinga certain aspect of the formulation, or delivery system, and then you'll have all that information, you'll be able to put that together, whenever you're ready, you can certainly wait till the development when the marketing application is, is going in, but you know, usually you want to put it together and start to build that sometimes people leave companies, fortunately, that inherent information might go out the door. So, it's always a good thing,at least in my mind, if I'm managing a CMC group, you know, regulatory CMC group is to kind of collectively start to build that again, story, as you see fit. Now, if there's no one to do it, well, that's a problem, right? Or if you don't know how to do it, that's a problem too. So again, it's kind of one of the reasons why there's consultantsout there or staff, you know, we can bring in some mid-level staff too, that have probably good foundation and ideas on how to build filings. Some people like the right as well, and some people are really good at it.

So, I would like to talk maybe some of the sections here, Meranda, in no particular order, you know, and this is just kind of coming up in my head here. But these are blogs that we kind of took out and put some information in. So, characterization is kind of, in my mind, one of the fundamentals of a product and a process and a program. If youdn'tknow what you're dealing with to start, then it's hard to catalog it make it consistently, it's hard to answer questions, if there's any analytical data, that's sure there's other stuff in it doesn't have to be 100% pure. But there are factors as far as impurities and things like that there's legal limits that, you know, once you run your preclinical study, you can have some dirtiness in there, you know, some impurities, but you know, you can't go backwards, you can have a pure compound and toxicology and safety study or preclinical studies, and then scale up your process or change your process where it's a very different impurity profile, because then you can see all the attributes that are in there that you can't determine if there's safety issues, or if that even affects efficacy. So you know, my advice on that one is, you know, go with the dirtiest material, you can, in safety studies and toxicology work, not too dirty, obviously, there's some standards out there, you need to follow but you know, and then try to improve your process after that. And by improving your process, having better control of it, maybe adding additional steps for purification, you know, you'll come in with a little bit cleaner material, that certainly should fit under the safety guidelines that you have established by the toxicology. So that said, sponsors have latitude, you know, to how data is presented, what's presented, like I mentioned, and how important messages are formed, formulated there. And that comes with data. So, if you have some data, you can tell a good story, if you don't have data, you make up a story, I'm kidding, you don't make it, you know, you have to have something honestly. And then where there's holes, you know, you have to be able to explain it scientifically, or, you know, you have to maybe commit to doing additional work.

So, it's a gray area, I won't get too much down that wormhole right now, because every program is different and talk scenarios forever here. But as far as authoring, you know, that that characterization section, there's standards, we talked about this a little bit just a moment ago, nomenclature, structure, General properties, these are things that are established probably early on, sometimes years, you know, years before, and when the programs are just sort of initiated in the research clinic. But you know, then you'll get into some of the more novel things, the elucidation of your structure, which you know, occurs at some point and then your impurity profile and, and that also kind of streamlines into your process, you know, you're going to want to know your impurities, before you get too far in establishing your process or setting your process. And that could be in the form of urine, organic impurities, these are, you know, started remnants of starting materials, any byproducts from the chemistry or the fermentation process, for example, on the other side intermediates, you know, that might be sitting there degradation products, that's another, you know, they could be organic, probably are, any reagents that you're going to use in the process, catalysts, ligands, those type of things like that, you know, you're going to want to make sure that you have a consistent material at the end of the day. And you're also gonna have an energetic impurities, he's gonna include reagents as well, catalysts, obviously, heavy metals, salts, other materials, also filters, charcoal, you know, things that fell into the reactor, I have good stories about working on a CMO or you know, accidentally things fell in and, you know, you're going to make sure you'll pick those out, but you'll see those would recommend going right into there, looking at some of the recommendations that they suggest, you know, you're making, let's see what you have. And then plotting these into some sort of plan, you

know, where you're going to do certain things, you might want to generate some impurities, you know, which could ultimately become your reference standards and stuff like that, during your process, you have to isolate them. So, it goes into that, that whole mix.

So, the next area, and this is probably in some folks mind, the most important, it's arbitrary, they're allvery important. Now, it's the manufacturing of the drug substance and the drug product. So if you don't have a process, you don't have a product, right, things don't just appear out of thin air, we have countless stories about you know, different types of chemistry, different types of fermentation, you know, changing cell bank, then having an upstream process that's, you know, severely affected, the titer could be affected. So there's a caveat of different things. And it's, you know, we can use the analogy, it's like baking a cake, and the cake should look the same at the end, but um, maybe a little bit more complicated than a cake baking. So, just to highlight some of the areas of the drug substance, you know, the manufacturer is pretty well established, you know, you'll be required to put some information in there that certifies who they are, and if they're GMP and where they live, and etc. But some of the other areas are important too. So you'll want to describe your manufacturing process, you'll have a process flow diagram, that's probably one of the most basic functions, a flowchart summary, right? And then you'll have this in the beginning when you submit an IND for the most part, but then you're going to build a story around that, right. It's a very creative picture and shows what the chemistry looks like but some of the questions that you'll eventually start to address in a submission and write up where necessary come out of thework to development work that you do. So, you know, you'll want to talk about robustness of your process, you know, do you have rework, are they common? You know, how did the physio chemical profiles of multiple lots compare you know, this is where you start to bridge characterization specifications with the process.

This could be at topic in its own right, but critical quality attributes CQA for critical, intermediate and final drug substance, right for drug substance side, right, you know, what are they? How did you define what they are? Why are they critical? Are they critical? And then that certainly goes into being critical process parameters associated with these CQAs as you know and is there data to support this association. So, all that story has to be put together, you know, has to commercial synthesis been defined, you know, there's usually there's very little changes later in the process. But sometimes there are, for different reasons, mainly scale up and cost and those type of things like that different, you know, you move something to a different facility, perhaps there's equipment that's different.
So you know, there's subtle changes, there could be, it's not advised to make major changes towards the end, because there's just a lot of bridge work that has to happen and creates a lot of angst, right, you want to, again, start to think about this, you mentioned earlier, you know, when you start to think about things, when you start to write things, you know, as you go through it as your business model comes, you know, as you know, how much material you're gonna have to, you're gonna need to commercialize, you'll ask your se questions, you know, your batch size, is it? Is it commercial, right, suitable process, hold points, those things like that, these are things that you'll learn down the road, right, as you do some of the development work, you know, how, how have these been determined? When should they be determined? Right, some additional questions that, you know, you might want to discuss internally with your CMO or just your, your, your staff, you know, are the reagents? Where are they coming from, we have, I guess, in the midst of a pandemic, here, there's supply chain issues, not just with furniture, for refrigerators, kayaks and those type of things like that I kind of found the last year but you know, sometimes starting materials, even sometimes reagents to use in the process, right. So along the lines, you'll eventually build inventory, you know, prior to doing this process, so that shouldn't make a big difference. But there are supply chain issues, you know, and then then going down to some of the control these materials, I can't emphasize this probably enough. And I think most folks probably are aware of regulatory starting materials, where does GMP that Good Manufacturing Practices start, right? So reg, reg is starting materials. And it's defined as the point where the sponsor commits to these GMP process. So you can have a 20 step synthesis, and you may only be required to have GMP in the last three steps, and in that case, you're probably going to look at your process and say, Hey, we have such a clean process, we get rid of everything impurity wise, in step two, and then the rest is just chemistry. And there's no you know, that opposed, if you have a three step process, and you know, the last process is still a bit dirty, same goes there, you know, you really want to find a point where you can establish where you know, if anything changes prior to that, it shouldn't affect going forward. So, and that includes changing reagents, changing starting materials, you don't always get the same starting materials from

the same supplier, you can have early in phase one, you can get your materials from, let's say, India, from XYZ CMO. And then because of the cost of goods and a couple other things, maybe supplier or just naturally, the amount that you need unit, you may get some different materials from Europe, and the chemistry to build those, those starting materials may be completely different in different regions, even different chemistry that can create a different impurity profile. So, if you think about it, common sense is like, if you have a different profile of some of those things, carrying that through to your API, you're going to have potentially different activities, you're going to decide your actions, you might have different material. So, if you can determine that you can use anything from anywhere at this point, doesn't have an effect on the final product based on your specs and methods, you're probably in pretty good shape. And to make a long story short, you know, that's probably where you would establish your, your starting material, or I guess we're starting materials.

Also, in this section, you know, the manufacturing section of substance and product, you're going to describe your analytical methods, you know, you're gonna have interim methods to test intermediates, you know, different steps of the process. And that goes for a large molecule as well. And sometimes they're just as critical as your final methods and specifications. And then in the write up here, you know, going back, I have to remember the odd couple here, you know, questions that you'll ask, and the difference is how you display them, or how you convey them to the FDA, and, you know, filing and could give them a little bit and kind of certify it and hold the rest for questions where you can put you know, a little bit more information, especially if your process is suspicious, or, you know, it's just kind of tricky, you know, where the processed impurities generated, which parameters influence these levels? Right, you know, how are the parameters that influenced this product, the quality here control, you know, do you have a good handle on that? Are they are these tests, reproducible? You know, you're going to get the same thing every time. Should, right, and then are there, you know, any correlations between these process controls and the critical quality attributes that we spoke about? So, that's your control of intermediates. Now, perfect timing, Meranda, you know, you mentioned something when you do certain things and write certain things, process validation, and this goes for substance and product, you know, the cottage industry, you know, declared many years ago that the that it was, you know, you need three validation batches. That's set, right. Yet nowhere in the regs as far as I know, does it say you need three batches? It may say it's some paper I don't know actually have to look back to this, but I don't think in the guidances, that there's any statement on number of batches, typically three is a good number, you know, it's, it's not two, it's not one, and it's less than for validation work cost, money and time. And those are things, you know, come to play, if you can do something three times in a row consistently, generally, that's validation, right? But this, this is where, you know, you won't be talking process validation for a while you'll have this in the clinic ministering to patients getting to a pivotal study, before you do most, in most cases, validation, because you're not going to spend the time or money on this, you know, until you know, you have a viable product that can be commercialized.

> “There are a few caveats to excipients. One of the things you’ll want to recognize and a question that might come up is ‘are they of human or animal origin?’ And the other big thing is ‘are they novel?’”

So, but at that point of validation, there's a lot of fancy guidances out there, a lot of large pharma sort of helped build some of these ICH, guidances. Because, you know, there's a lot of process and formality you can put into them. The truth is, though, small emerging companies don't necessarily do that, you know, they, they have a requirement to do process validation, and they do it on a budget and pretty efficiently, you know, based on the requirements at the end. So This usually happens in phase three, you know, somewhere along the phase two, you know, you're goingto generate a validation master plan or protocol that has yet objectives and scope, responsibilities, outlines, you're going to work through this with your vendor are going to come to some agreement and certify this and then you're going to, you know, exercise it and do the process validation. But in that process validation, you're going to, again, critical process parameters, right, these variables, and then

associated ways you're going to sort of measure and follow, you're going to want to document this during validation work. So that could be phasetwo, but more or less, it's sometimes phase three. And I should bring this up, sometimes, in certain part with products, you know, there's no validation required until you're actually going to ship the product. So, it doesn't necessarily have to happen prior to your submission can happen during your review, it just has to happen at a certain point. And there is a guidance out there that's slipping me right now. It kind of sort of outlines this, it's actually not guidance, I think it's actually a it's part of the CFR that gives a little bit more information. But check the FDA, his website, I think we mentioned in the blog, too, but it talks about timing, you know, we obviously want to push off most of this work that costs money until you're fairly far into your review, because you know, anything can happen in a review. Most folks Try not to do validation too much prior to your submission. Sometimes they do though, sometimes the validation batches or your stability batches. Sometimes they're you know, part of the trial, the phase three, it depends on really how many, how much material you need, the population that you're going into all those things like that.

And then you know, one of the other things again, justto finish off the substance section here that process development, this is the conformance information, you knowwhy we did this, how we did this, it's not necessarily the nuts and bolts details, but you know, it does tell the, the abstract story, you know, you should be able to read section s2 6, and come away with really a visual of whathappened over the course of drug development, you know, from the beginning, actually to So, you know, as certain things fall off or become irrelevant, you can take them off. But it's a great thing to have a story. You know,we started here, we did this, and this is the reason why now we're here, we did that. And it you know, culminates with that section, you can glance over at your process, some of the other sections in there and you go, Okay, now it makes sense, right. And then, same thing, you know, I'm a drug substance, person by training background, so I sometimes forget the drug product, but same thing, you know, you have manufacturer, that you're going to have a batch formula, you're going to have a same type of things in the description of the process, you know, the, the flow summary, right, and then you're going to build some of that information. I'll talk about your process controls, you know, same thing with critical attributes and parameters and things like that, you're going to touch on any information on excipients. This is a big thing for the drug product. Outside of the API, you know, these are pieces of materials that are put together in the formulation to either keep it stable, to deliver it, you know, various functions, these are not part of your original API, right, they're going to bite you in to buy these, you're going to want to make sure that these are, you know, legitimate, safe. And there's things like that, again, a lot of information on excipients, on the FDA website, and we did have a nice section on our blog. And then just to quickly finish off some of the, for the audience here, critical steps and process intermediates, same type of thing. As I mentioned, I don't keep going through this with the substance, but a little bit different, right, you're making something you're putting into a vial, there's just a little bit different than just the chemistry in a sealed reactor, right. And then the validation process validation, same thing, you know, you're gonna have timing on that. You may not do that until after you submit your marketing application. But there is a requirement to provide, you know, have a protocol in sight to for inspection, and then ultimately deliver some of this data to launch the material to sell the material.

Meranda Parascandola
Yeah, that's definitely the largest section for drug product and drug substance. A lot of information goes into making those.

Ed Narke
Yeah, so we talked about the excipients. Right, do you have any questions on excipients? There's a lot of questions for myself here.

Meranda Parascandola
Yeah. As far as excipient. I mean, I say do your due diligence to make sure that the excipient like you said is qualified and up to the standards of the FDA EMA. Don't just take their word for it. Make sure that you havedocumentation on that I believe excipients Do or do not require a drug master pilot,

Ed Narke
They might have the others, there's drug master files for filed for excipients. That's a quick way to reference the

Meranda Parascandola
Yeah, exactly. So then they should have an open section that you could review and look at that and utilize that for some of your backbone for your excipient. Right. And

Ed Narke
Then you'll get specified via specification, you know, acceptance criteria, they'll have specs and methods. And, you know, these are not necessarily critical to the drug sponsor, but you know, whoever manufactures them, it is critical to get again, going back to the consistency of what you're providing, if you're buying something here, you know, if there's changes to it a bit through a process, or just the level of impurities and stuff. And as excipients, you're going to want to take that into account. So again, same thing goes along the lines, and we'll get to the control of the drug substance and process and product sections in a bit. But while we're on excipients, and since you mentioned drug master files, there are a few caveats to excipient. So like one of the things you'll probably want to, you know, kind of recognize it's a question that will probably come up. So, you know, you'll want to know it, you know, are they human or animal origin, you know, this, this has a big bearing on the safety profile. So if they do come from animal origin, now, it's infrequent that they come from animal origin and maybe a human origin, but sometimes they do. And then the other side of it is the other big thing for excipients. To think about as if they're novel, there's a quite a nice description on the FDA website, you know, if it's an excipient, that hasn't been used in another product, which happens, for various reasons, you know, it may not have been necessary in other products, but there's a new route of administration or type of NCAE, that would require a different type of excipient. And also levels, you know, sometimes the levels are established in certain programs, if you're dumping in twice as much, or, you know, whatever, you would have to take that safety consideration. So just a whole litany of things to think about if you have novel exceptions. And, you know, basically, the definition is new excipients are novel excipients, or any active ingredient, active ingredients, when I say, that are intentionally added to the therapeutic, you know, but they're, they're not intended to exert therapeutic effects, you know, they're not an API. And they're, they're not fully qualified by the existing safety data with respect to the current, you know, proposed level exposure that I mentioned. So, you'll have to do additional safety studies, and there's, there's additional work that's going to have to be required. So if you have a novel excipient, and you don't have the drug's master file, in most submissions, you have to create another module three, you know, that has the same type of information, the process to make them, the control of them how stable they are, you know, you'll have to put a little more effort and write up into some of that, if you have an excipient. So that's one of the things to ask yourself early on.

So the analytical control section, and the analysis and reference standards, I'll kind of hit these all one, one sitting here, we started to make some references to some of this, you know, how you control it has to be the same every time, you know, so the link between this product specs and methods and stuff makes intuitive sense, right? You can't change, one can't change without affecting the other. So obviously, if you implement a different method, you know, the specification will be different. And those are things that I think thatyou know, it really depends on your program, but quite important. So, product specs, list of test references to the procedures, and associated acceptance criteria to range or level. Other standards that are used here come into play as well. So and some of these are related to the critical quality attributes, sometimes a critical quality attribute is a specification to kind of go through these typically there's a list of things just associate it with any type of product, for example, you have a well characterized, small molecule that's made by a chemistry process, a synthetic process, right, you're gonna have a quantitative statement or description, you know, it's this, it's this color, it's a powder, those are things just a quantitative description that you know, you're going to want to put together, there's other things that you're going to have, and that's based on, you know, your program, but identification testing, there's a few requirements are going to require to two separate specific identification tests. And usually they're run by HPLC, one of them and an IRR method. They're very established analytical technology and methods out there, you know, and the most common specification is your essay, which is essentially it's the level of your active so 99.99 is always a good number. But, you know, there's ranges, you can have something or a spec set at 95 to 105. Again,

this goes back to qualification of your material and safety studies, how reproducible you know, your processes, manufacturability, you're gonna want to kind of come close, you know, to that same essay, each time if there's variance, you know, obviously, you're gonna have questions.

And then the other part of the methods I think, for most programs is HPLC. That's the basically your liquid chromatography to basically measure your impurities, you know, you're going to want to scan your product to see what's in there, right. So you're going to have different methods, mainly HPLC and these all pertain the SH PLC, ID testing. These are pretty much for all programs, but you know, a lot of actives might be different. Some instances you want to measure part Size melting point, you know, LOD, loss and drying you know, you want to do Carl Fischer to see how much water is in there. Sometimes it has effect on the drug product and formulation, right you'll, if it's the solution pH, you know, any microbial events, when you're talking about, you know, maybe this is more on the product side. But if you have a sterile product, you know, you're going to have different specs in order to control that to ensure that you're not getting microbial effects, or any type of that type of work.

The rest of the sections, again, don't want to speak too much about analytical procedures and validation,we do have a podcast, right, where we talk to Colman Byrne and the analytical team, and it's really great. He, you know, kind of his 30 years of experience with working with procedures, validation, you know, the hiccups that happen, sometimes some of the other areas that are required in this section are batch analysis. So you'll have a, sort of a history of all of your, all of the materials that you made, you know, kind of with all the information, a lot number, what the date where it was made a scan, you know, you'll have the last say, for each of these, you'll have additional information like the impurity profile, I have a great visual, I don't know if I can share it here. But I put this together, probably in the early 2000s, just an evolution, I worked at a large pharma and there was probably 15 years, there was 50 batches made. And you can see the evolution of, you know, very simple specs up in the beginning, very little information, very, you know, additional testing and stuff like that, as that was scaled up as that was transferred. And, you know, multiple sites for making it, you know, as they become became much more specific, you know, there was actually a second essay on orthogonal acid that was generated, but you could see additional information was tested over time, additional methods were put into place. And in some instance, for stable product, you can, you know, run some older material in current methods with current specs to see where things come out. A lot of times, you know, some of the API does have a shelf life, so it may have degradation over time, so you can't tell if it is the same. But you can certainly show that, you know, that if it is, then you have a pretty stable process, one of the kind of most touching, in my opinion in the section at least, and we could do a podcast on this one as well.

And kind of one of my favorite actually are just because it's so interesting how you can put this together, justification in your specifications, right? You can aspects, big deal, right? You have to be able to justify them, especially, there's questions. So these will these will provide, education provides comprehensive control, and, you know, identity and purity and things like that. So, early in development, they're controlled, you know, anything like the sending, the specs are controlled by a qualification, qualified, qualified method, and then you want to validate that, so in phase three, you're gonna have your draft final specs, and they should be justified regarding the historical experience. So all that work that you did, you know, up until that point has to be integrated the manufacturer ability, why you chose certain methods, why you set specs, etc., right.And in phase three, you know, the drug process should be well defined, and openness changes. So that's where you're going to establish your, your, your reasoning. And since specs are chosen to confirm the quality, rather than to characterize the product, as sponsor should provide the rationale. So just to finish off that, you know, consider answering these questions, you know, are the specs linked to a manufacturing process? And why right, are should they account for the stability of the drug substance? And how do they are they linked to the preclinical and clinical studies? You know, are they linked to analytical procedures? So, if you have a process, and you have stability data, and you have, you know, preclinical studies, you can relate all this, you know, the story back to that, right. So yeah, we set the spec because blah, blah, blah, we had preclinical studies that were in this range, and etc, we did qualification studies, you can set them based on the sensitivity of your methods, your procedures, those type of things like that, to show that they're, they're set properly. And, you know, manufacturability that's

one reason I think I can throw in here that you don't want to set tight specs too early, because as manufacturing changes, you know, you may find yourself out of spec. So that's just part of the process.

And then you know, samething applies again, I probably don't do a drug product sections justice, even though I wrote tons of them, I just never really worked in the manufacturing area. But you know, you have the same specifications there. You'll have description, identification, essay, purity, profiling, right, you're then you'll have based on your based on your dosage form your formulation, different types of additional specifications, disintegration, dissolution, moisture, again, viscosity, again, you know, there's a volume of fill, and those type of things like that same thing with the procedures here, you know, it's very similar to the substance, sometimes the methods are the same as the substance, if you're measuring the essay, for example, you may have the same method in place or the impurity profile, the same ones in place, maybe a different way to make the samples, maybe some different reference materials or different instrumentation. But you know, along the same lines, you're trying to control the process and product testing, we can get into this and another area.

End product testing is really the game. It's quality by chance, as they say, QVC. There was initiative A number of years ago, it's still in play, I guess the quality by design, as you know, testing product quality and consistency into your process, right. So this way, you're not surprised at the end quite expensive, though. There's a lot more work and data that needs to be generated. So typically, folks don't fall back on, you know that that final test series of specifications and methods if you meet that, you know, you're good. But we'll, we'll talk and maybe in the future about the evolution of that, and then the same thing justifying the specs, right? We talked about that, you know, why does it have something to do with the process, you know, you said it this way, because you can consistently make it this and these range, does that have something to do with stability are some that some of these methods and specs are stability indicating a lot of the methods I was going to mention it earlier later, actually, but you know, a lot of the same methods are used and specs are set and for the stability, so as long as you're measuring a server time, you know, you should stay within those ranges. And I'll just touch lightly on reference standards, you know, very, very important, fully characterize your reference standards, or elucidate structure as early as possible and save a good amount of material, because that's what I found in my career, you know, there's always missing or we ran out of reference material, and that becomes a bottleneck, and you have to make more is the same as the original one. And if you have different reference materials, you know, over time, it's hard to correlate data previously, you know, you're gonna have some variability there. So that's about all I want to say on the analytical process section. Again, some folks think this might be the most important and I think there's relevance to say most of these are in it, depending on what technical functional background you are, or where your holes are, you know, I think that's one thing maybe kind of we can agree on. The most important sections are where you have the least amount of data. So, container closure, packaging is substance in the product, you know, quite important, because you're trying to keep consistency. If you have powder, you know, lying around, if it's hydroscopic, you can pick up moisture, degradative, whatever. So, you know, typically you're going to have in an API form, you're going to have a bag, certain type of material inside of a drum, sometimes sealed, sometimes these materials, these API's are light sensitive. So, you're going to have different types of things on the drug product side, you know, packaging, primary packaging is your, if you have a vial something for example, like that, it might be a second put into a secondary packaging, again, maybe for light sensitivity. Those are things I can cover here briefly, do you know anything about packaging or do you any questions on

Meranda Parascandola
Packaging, in particular, I mean, drug substance, I don't have a lot of experience with I know that there is various different drug product packaging that people want to consider, depending on the product, of course, you're talking about an injectable, of course, that would be a glass file. But when it comes to certain types of plastics and stuff, I know that there is leachable issues, stuff like that, and, you know, vials to consider and the headspace as well, stuff like that, for my understanding, you have to really think about the container that you're going to use to house your drug that make sure it's compatible with your drug and doesn't affect your drug?

Ed Narke

Yeah, so for the substance, like I kind of described, there's a, there's a drum, there's a plastic insert, you know, keep the dust down, or whatever. So but you know, you're going to want to provide a full description of the primary packaging for the substance and the product and the marketing application, you know, how it's stored, where it's stored, what the components are the materials, the chemical, and the physical reactivity of any substance, you know, it's kind of dictates the type of packaging needed. So, I won't go into it. But if like I said, if it's, if it's absorbing water, you know, there's controls that need to be in place, if it's light sensitive, obviously, right. And then you'll also do some minimal identification testing on this packaging, but I'll leave that to another time, the secondary packaging and we touched on that same with the drug product, you know, cardboard box is considered that secondary packaging, if it provides protection to the product test results of any stability studies has to be done in that that type of material in that container closure to show that that's actually helping with the stability. And, you know, kind of makes sense, right? I don't know, if I have anything earth shattering around container closure, I must say, this is one of the more dull sections in my brain, you know, from working on it very, very clean cut, not to mean, it's, it's simple. I mean, you know, obviously, if you're going from a sachet to sort of a bottle, or if you're putting something in, you know, some sort of different packaging, and trying to correlate, you know, to some original early development work, it's tedious, something that can't be taken lightly, and it changes any, any changes to anything in the program, process wise, or control wise, late in the game is it could be a problem, right? Because you're gonna have to generate additional data, because there's an unknown, you know, what does that change mean? Right. So, but that's kind of the synopsis.

> "Any changes to anything in the program – process-wise or control-wise – late in the game could be a problem because you're gonna have to generate additional data. There's an unknown there. What does that change mean?"

There's quite extensive bits of information on the ICH website on container closure. And so, it is a nice segue into the stability section, which you know, I think, probably pretty important. You know, it's one of the main questions that you get, how much stability do we need? Right, you know, well, it's just, it's established, you know, you need two years, if you want a three year shelf life, if you have one year and you know, maybe you have a little additionalinformation that you can extrapolate, maybe get some buy in, I think the thing is that, more importantly, is when do you have that data available. So, stability is one of those sections where you do get a little bit of leniencywhere you can add a little additional information at some point during the review without putting the review on pause or restarting the review.

So, you're going to want to have, in my opinion, you know, at least one year solid stability with your methods, validate methods in place, you know, just to show some authority and then you're going to want to have additional stability is to support extending that. So if you have a product that's been on stability for four years, and it's rock stable, and you're using the same protocol and the same tests, you know, you might be able to get away with being able to submit, you know, just one year, or maybe less, but it also depends on the nature of the product, if it's a must have, you know, an unmet need, maybe there's some leniencies a lot of times there's not, though, you know, it's this is where a conversation with agencies is important, you know, letting them know that you may not have enough data, but you'll still be generating it, you know, that sometimes there's binding agreement that that's allowed, right, sometimes, you are allowed to maybe make a small update in your filing, once it's under review. And I've been, I've been involved

with some circumstances where, because of the important, such an important nature of the product, you know, such a population that's affected, that's, it's just there's nothing out there for them.

It's called breakthrough designation, there, there's an allowance to maybe file information in your IND, under, you know, as the files review, just to show that there is consistent information generated to show that this product is stable. And if you're able to get that agreement, and you can, you know, update that IND over the six months or nine months to, you know, as that review happens, it gives some assurances without affecting the FDA's to do for process. That's right, because anytime there's new information, there, you know, there's a kind of sometimes you have to go backto the beginning review things because it does change the way the reviewer looks at things.

I know, I know, you love this conversation, Meranda, I just keep talking about you know, submissions, and what goes on them to highlight on a high level, at least right, it would take a long time if we really get into the weeds. But that's why we have our blog series. So you know, anybody that's interested, maybe take a look on our website and kind of check out some of the things. We don't have case studies on there. But I think I have enough elements that I pulled from guidances, and just experiences that could give you a sort of a high-level roadmap, and also contact us any burning questions, we can certainly have a consultation and talk about our experiences.

So last, but not least, is the composition and the pharmaceutical development modules in these pretty much relevant for the drug product section of Module Three. So, you know, again, you have latitude on how the status presented, especially in P2 your pharmaceutical development section. Now, to touch on it, your composition is just a listing of your active and anything in or associated with your drug product. And that includes sometimes processing agents, but mainly with your excipients and your active form, you're going to talk about maybe some of some of the ingredients, any solvents used in the process, you know, how the formulation was categorized? The functional aspects, maybeof each component, you know, why are they in there, and their reference points, you know, to for a viewer to examine, you know, to get a better understanding of how the product works. So any understanding of these components, you know, allows for data driven risk assessment during the review. And then when we were talking about functional x aspects, I guess I can define that a little bit better, four basic categories, right. Are they there for the stability of the drug substance? You know, are they there as physical characteristics to help that that, you know, did they help with absorption, maybe, for example, or manufacturer ability, you know, some of these are putting into certain, you know, tablets and capsules, for example, emulsifiers, and those type of things to help build the actual formulation, right?

In the process, you're going to want to discuss any impact on stability, new formulation, maybe there's some impact, right, some of these excipients, or stabilizing agents, and as mentioned,you know, how does that affect the actual product, you're gonna want to talk about the physical roles, the excipients, and the in vivo effects. And then you may have some in excipients, that using a manufacturing process, again, this is kind of just a one to three or five page sheet that's just going to have a summary of what's happening, right. So let me turn my attention to, in some people's mind, the most important section, P2: pharmaceutical development. And I'll try to give this a little bit justice here, but not being a pharmacist, or formulator, or pharmaceutical scientists example. I can't get into this technical function, you know, and I can tell you exactly what everything needs to be in there and what that data is, but I haven't made any of this, my career relied on a lot of other folks, folks that we work with today that you know, have been formulation scientists or pharmaceutical scientists for their curves. So, you know, this section provides any science, you know, science background rationale, for why you have that formulation, you know, through the final development and justification of that, that dosage form that you're talking about. Right? So any discussion in this section should cover you know, your solid or your liquid, whatever we have, including parenteral formulations. Guidances describe some, you know, they're only limited detailed with the requirements are so it's really more of a story. It'slike the manufacturing development section substance. It's really the story of why you chose this formulation, how you make it, what went into that, you know, how, how it's going to affect patients based on how it's delivered, you know, how it's going to be affected itself by being stored over long periods of time and such so you'll have a discussion around the components, you

know, you're going to talk a bit about the drug substance, you're going to tie this back to your drugs sections, you're going to talk a little more extensively that more and more the conformance information about excipients. You know, the excipients, if they're if they're grass, generally recognized as safe, your excipient section, like probably should mention this to mention previous mention of excipients was really the nuts and bolts, how you make them how you control them. But this is really why you're using them, you know, how you're using them, and those type of things like that, you know, I won't get too far, but you know, this, this P2, have different story, depending on your formulation, you know, if you have a solid dosage form, you're gonna talk about incompatibilities of the substance, you know, the functional groups and excipients that they exist, you know, any reviewing any fundamental chemistry and the excipient. If there's any activity there, you know, RNA the potential and capacities apparent or transparent, does that affect the quality, right?

And then you can get into solid state reactions and those type of things like that. So, it really depends on if your dosage form. So, if you have a liquid, you're not thinking anything like you would if you had a solid form, right? In this case, you're going to talk about different things, you know, solvents that you're using, thickening agents, to key lighting agents, antioxidants, for example. So for liquid formulations compatibility studies, also occur, you know, how do they interact with those type of things like that, right? Powder fill systems, like, what would you want to talk about there something about your process, right, compatibility again, andthen we mentioned, I mentioned this a little earlier, sterile, sterile products, you know, liquid dosage forms, stability is pretty important, you know, when you're autoclaving, but you're going to want to come up with well documented development efforts, information, you know, to defend the need for any for formulation, I can't, you know, be sterilized, if it's heat sterilized, and how that affects the quality.

And then for non-sterile liquids, you're going to want to ensure, again, like I said, the earlier the acceptable microbial bioburden, because, you know, youmay have a safe and efficacious medicine, but, you know, it could potentially harm you because it has microbials. In it, that's probably not a great thing, right? P two, three, manufacturing process development. You know, this is again, like the related substance section, you know, it's gonna be a discussion of the process development, you know, why certain things were made, this is the conformance section again, versus like a compliance section, which is a description of the actual process. So you'll talk about your experimental designs here, you know, your understanding of the process, any attributes, again, critical ones as well. And then you could do a hazard analysis or you know, the type of things to find a criticality. This is where you would discuss any reworks, you know, how that operates, how that happens, versus throwing your materials away. You're going to touch a little bit more on container closure, and P two, five, again, we talked about the compliance section. Now, here's your vial, here's thespecs, here's the seal, here's the cap, here's what they're made of, etc. You know, for here, this is where you're talking about if it's if it's an oxygen, oxygen or moisture sensitive product, you know, you're talking about the package, why you chose it, you know, that provides the effective barrier, right? And etc. So this is the conformance section, you'll touch on the microbial attributes and the compatibility as well in this section, and I won't get too much into those areas. So.

So Meranda, there you go. There you have it, the odd couple, definitely different techniques and philosophies and cultures out there. So you know, you have to do what's best for your program. You have to be able to sit in the chair and defend it when you get questions. Yes, the main thing is you try to avoid any questions. So on that note, hopefully you have a wonderful Valentine's day this week, you'll see lots of red, I'm sure some places. Anything else to finish off with?

Meranda Parascandola
No, that's, that's it. Thank you so much. And I see you're wearing red today. So, it works out well, of course.

Ed Narke
For folks that can't see me I'm wearing all right, except for my hat. So let us know what you guys think about these topics. Again, as always, we love any feedback, you know, hit us up, we'd love your comments, if you have them get

in touch with us on their website, you know, we laugh, we like to make friends, etc. You know, very important note as well, you know, please subscribe to our channel, if you already haven't, you get notified immediately, when the premiere of the next CMC live is out. It's one of the only forums out there that I know that we talked about things, you know, engage with us, perhaps, you know, send us questions. You know, I'd love to get the chance to chat with most folks emerging biotechs out there, I love doing it. You know, I love learning about their programs, and I love sharing my experiences. So, likes go a long way. You know, we want to build more likes, we want to build, you know, more of a resource here. And we, you know, see most of our other content, prior podcasts on YouTube. Great reads great listens if you have them. Tell your friends about the channel, Spotify, Apple Music, wherever you get your podcasts, we are going into our second season. So, any ideas that you have, you know, send them to us, we can bring in the right people, a lot of good technical folks here and also, you know, our network outside industry will start to build so it's an amazing thing. I'm having a great time. It's Valentine's Day Meranda, right. Celebrate. See you guys next week.

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