Effective Strategies for Early Stage Drug Development with Judy Magruder

Episode 3

Ed Narke

Good Morning everyone. Welcome to CMC Live, I am your host, Ed Narke. On today's podcast, we're going to talk about "Early-Stage Drug Development. What's the Secret Sauce?" So, you are an emerging biotech company, and you have just begun the development of an in-licensed product and/or just received initial funding. Now the fun starts as you sort through what R&D has been done and you start to prioritize a long list of ideas from your investors, board members, scientific advisors, and your team. If you are a virtual company, there is the added feature of coordinating a geographically dispersed web of CMOs, CROs, labs, and experts into one cohesive team. You will need to decide which of the ongoing activities can, or should, continue while trying to cope with coming up with the concise set of long and short-term milestones, and a plan and a budget to go along with that. As you dig in and get going, you realize that the company wants to keep the spending to a minimum until certain pre-clinical or clinical milestones are met.

> "There's so many different ways to communicate what's important, what's the critical path, what are the milestones and what's important to focus on today."

So, what would you like to get accomplished, and what will be funded are not the same thing. How do you handle the product development? What drives the decisions to do or to delay? What risks are associated with that? How to mitigate these risks and lobby for support? When do you approach the regulatory agencies? And how do you do it with the best package possible? How do you build and manage a realistic plan to balance funding, resources, and risk, while maintaining flexibility to adapt to new data, funding changes, regulatory input, market forces? Just to name a few.

Today, we are chatting with Judy Magruder, live and virtual from Mountain View, California. Early-stage product development champion, horse owner, hopefully still an all-around, fantastic person that I have met many years ago. Judy has a lot of experience with what we just went over here, and on this podcast, we plan to have a great discussion on sponsors that are in this situation. Welcome Judy, tell us more!

Judy Magruder

Thanks for the intro, Ed. I am happy to be here talking about my favorite topic. Where to start is a great question. I very often meet with early-stage companies that either have just acquired a patent or a scientist has had a breakthrough in his or her lab, and they think, "I want to bring this thing to market. What do I do?" Often, not a lot of drug development experience and just trying to figure out where to go from there. I love those situations because it is kind of a clean slate. I encourage these folks, whether it is the company founders or initial angel funding investors, just to think about what the product would be. What are the various registration strategies? How do you get this product to market? What would it look like? What label would it need to be? I encourage

them to think there first, and then back up, and build a plan from there. When you look at a product like that and you start thinking, "Okay, what are the market forces? What is the competition?" All the way from financing that you need, the science, and the regulatory. I suggest thinking of the big picture first, and then all the minutia and the smaller, what I call “the micro-plans”, come later. I think when companies take the time to do that upfront and build a registration strategy, “what does the product need to look like when it hits the market,” all the plans underneath become that much more valuable and realistic.

Ed Narke
Even though there's funding out there, there's limited funding as we know, CMC sort of takes the backseat to the clinical part of the program. From what you mentioned here, what is the prioritization of some of the goals that lead to some of the decisions that come about? Can you maybe talk about some of the steps to building the most useful plan, based on limited resources, time involvement, and satisfying your stakeholders?

Judy Magruder
Absolutely. Well, I think once the team has spent the time thinking big picture, they need to think about what is that critical milestone they need, typically for the next funding round. Because, at the end of the day, business drives so much of the science, fortunately, and unfortunately. Once that milestone is defined very often, early on, it's the IND. How do we get the IND filed as quickly as possible? Well, then you break it down into the three major buckets: there is CMC, clinical, and non-clinical. I think of those as the major buckets and think, "Okay, what are the key things I need to focus on for each of those?"

“Think big picture first and then all the minutia and the smaller, what ‘I call micro-plans,’ come later. I think when companies take the time to do that upfront and build a registration strategy, ‘What does the product need to look like when it hits the market,’ all the plans underneath that become that much more valuable and realistic.”

So, early on it is typically non-clinical and making sure you've got a safe product and you do the appropriate efficacy and safety studies, but you need API to do that. CMC goes in the front. They start making some material and focus on how to make appropriate material for those early safety studies. And how do you do that quickly, cheaply, and safely?

So, you look at the risk. What do you know about the compound? What do you know about synthetic route, impurities, those kinds of things? Make sure that you design safety studies that address those risks. Early on, it is a lot of interplay between the toxicologist, and the safety folks, and the science folks who understand how the molecule works in these non-clinical models, and then we need to make material and test it in safety studies. Those are the typical early-stage activities, but then clinical also have to kind of sit over on the side and say, "Make sure you're testing safety elements that will address how this product will be used in the market. Look at any non-clinical hits it might have in terms of a safety signal." I need to know that stuff up front, as well. That's where the integrated project plan comes in, all the different components of how you develop a product need to be thought of from day one.

Ed Narke
Right. Okay, joining us again today are Brian Lihou and Meranda Parascandola. Brian, any questions? One of the things I was thinking about when Judy mentioned, how do you stay on track? As we know, you have a plan set out, you have some financing, you make some decisions. It rarely just goes like that, right. There are always some things that come up, new information. Judy, or maybe Brian, you can add here. How do you stay on track?

Judy Magruder
When I work with folks, I am one of those people, I love Gantt charts. Most people hate them. I use them as tools. They help so do some scenario analysis. I rarely put them up in a meeting or a... It is just a no. People's eyes glaze over.

But I use them to look at different scenarios. So, when the team has done the initial work of the global strategic plan, if you will, kind of the big picture, then I break that down into different scenarios and say, "Okay. Well, we could get to this milestone any number of different ways." I use Gantt charts as a tool to create scenarios, “okay, here's one scenario, here's another.” In each of those scenarios, there is a critical path, which is the one holding the plan up, and there are different risks. We do those analyses of which risks can we stomach, and which ones we cannot. You pick a scenario, but those little micro plans underneath the big picture are never static. You are constantly looking at those micro plans, you're updating, because there's new information all the time. In this business, the one constant is change. That micro plan is never static, it's always changing. But the goal is really to keep that macro plan intact, that milestone you've identified as valuable for the company. The challenge is in that, each of those micro plans for the different disciplines, how do you keep your eye on that goal in the macro plan? There's a bunch of different ways to get to your goal and just don't change the dates. Think of a different strategy or manage your risk a different way, but do not change that date.

Brian Lihou
You have many different stakeholders and in smaller companies, those are defined. Some people are very passionate in the aspect. How do you have them buy into this holistic Gantt chart approach because oftentimes you'll have very defiant personalities? As I said, it's passion, truly driven from passion. How do you get that buy-in and work through those spots that make Gantt charts that see the entire project sometimes difficult to use? How do you manage that?

Judy Magruder
Great question, because people do get passionate about their discipline and say, "I need to do this animal study. We cannot proceed. It's not safe unless we get this data to move forward," or some CMC impurity study, pick your example. Which is great because those are the people you want on your team. I encourage people to step back, “okay, let's look at the big picture again.” Let's remember that the company made a commitment to have an IND by this date, and investors are really... You know the company needs to move forward. Put that aside and say, "Okay, there's a bunch of different ways to get there." So, if we need to do this safety study, for example, that's going to take 10 weeks longer than we thought, what can we do to get material sooner, so that we can condense the overall timeline? Let's look at CMC options that give us suitable material for that study sooner, realizing we have to do the other things to create material, for say, the GLP-tox studies. You remind people of how their piece fits into the bigger picture, and while not minimizing their concerns and saying, "Yeah. I hear what you're saying. We need that safety study, but we also need to meet this milestone. Let's figure out how to do both."

Brian Lihou
I think in pre-clinical it's important because things are in such a state of flux. The later phase you get it's somewhat black and white, the steps you go through to get to the next phase. But in pre-clinical, I think what you mentioned is important, that creativity and flexibility of getting to the same endpoint. That's where I think that visual aid of a Gantt Chart, even for the non-believers of Gantts, they'll see the interdependencies. They'll see the linkages, and it helps them understand how their role is important to the end product. That's a good point.

Judy Magruder
Exactly, yes.

Ed Narke
Okay, you have a team. You're talking about a small biotech company, for example, maybe licensing a molecule out of academia, or licensing something from a larger pharma and getting some funding. Kind of just hitting the ground running. Most of the time, they may not have the supply chain or a lot of data to start on. So, this team, even more so today being virtual, you have external vendors. Their business model is to make materials, they don't necessarily know what your goals are, where you want to license your product, or how far you want to take the development. You have individuals, consultants, or some short staff, covering a lot of different things. They may be virtually located in different time zones.

Can you tell us a little bit about an effective way to execute a strategy? You mentioned that it's always changing. How do you execute the strategy shifts with this virtual team? Emerging biotech are known for that, everything's pretty much outsourced. Things change and milestones are redefined. Can you talk about some of your experiences with smaller early-stage emerging companies, essentially, one product in development, and when these types of things occur?

"Things change all the time, and so whether you do a weekly meeting, or a daily meeting, or a sub-team, I just let people know, number one, what the change is. Communication is the key because it's so multi-disciplinary. All these different disciplines depend on each other, so communicating change in a very succinct way is important."

Judy Magruder
Sure, absolutely. Things change all the time, and so whether you do a weekly meeting, or a daily meeting, or a sub-team, I just let people know, number one, what the change is. Communication is the key because it's so multi-disciplinary. All these different disciplines depend on each other, so communicating change in a very succinct way is important.

You can start your team meeting and say, "We got a safety signal. We need to look at the CMC route and get rid of a couple of impurities or figure out which caused the problem, so let's shift gears." Then everybody understands why we're shifting gears, and then you can say, "Okay. What can we do?" Typically, I won't present a Gantt chart, I'll use different graphics and say, "Okay. Here are three boxes that connect." I'll put a little line and show people the critical path.

Then they can understand why we need to make a shift, what the new ground rules are, the end date, - you hope to never change that unless you absolutely must - but just make sure people understand what's moving underneath that. I find that once people understand why they need to make a change and why something new may be important, as opposed to something else, they get on board and then we focus on just that critical path. If there are five other things underneath it, that we know right now it looks like we have time to do, I don't even talk about it. It's like, "Let's just talk about the critical thing, all that other stuff will happen underneath. I know you guys are professional, let's just focus on the key thing today."

Ed Narke
Okay. You talk about Gantt charts and they're well-known in the industry. Everyone loves them, of course, and they're very useful if you apply them in practice. Any other communication tools early-stage companies can use to improve the chances of keeping to their strategy, being adaptive to change, or meeting milestones?

Judy Magruder
Yeah. I find that when companies go out looking for funding, or talking to investors, or talking to the market, obviously they have a deck. There's the slide deck that you create, and within that slide deck, there are graphics

that they use. I like to use those with teams, just so that teams can see how the company's communicating to the outside world. Those are typically much simpler. They've got a couple of boxes or just dates, sometimes it's not even a timeline graphic, it's just a table. So, I like to use those, I use various PowerPoint formats.

I've been known to have used five or six different formats with a team until I find out what works best for them. Every team is different, some people are visual, and they see things differently. I like to try out Excel graphics, PowerPoint graphics, modified Gantt charts, calendars, tables, etc. There are so many ways to communicate what's important, what's the critical path, what are the milestones, and what's important to focus on today. I play around with a lot of different designs. Often, it's tables, here's the task, here are the dates. People can't look at graphics, they like those. So, I try a lot of different things until I find out what works for a certain team.

Ed Narke
Not to take you off the spot Judy, but I have a question for Brian and Meranda now. So, Brian and Meranda, you guys are speaking with a lot of early-stage companies looking for a supply chain and looking for a path forward in the strategy, while at the same time looking for money, partners, and those things like that. They're not necessarily focused on the CMC. Can you share some of the questions that you get at that stage, maybe folks that aren't necessarily a background CMC or technical, but they do have a flavor for the drug development process? What kind of questions do you get early stage in a Pre-IND going into IND companies? Perhaps, Judy, we could play a game here, you could be on the other side and sort of answer some of the questions based on some of the work that you have done.

Judy Magruder
Sure.

Brian Lihou
I would say the biggest challenge is when the sponsor does or does not accept the fact that some development work may have to happen. Everything worked just fine on the bench, but when they move it to a CMO who caters to the small-scale pre-clinical or early phase clinical batches, there is a certain amount of development that needs to be done to make sure that process is transferable. Yet, you have people, on the sponsor side, that just simply don't see that. They see it as an opportunity to have to spend more money. Now, we tell our clients that you don't have to have a perfectly characterized process. You don't. However, you do have to have a process that could be made the same way twice. So, how do you manage that, Judy? Again, a lot of things are driven by the dollar, and you have to respect that, especially with smaller companies. But how do you manage that balance between essential development, particularly with methods, and understanding the big decisions are driven off those methods? How do you manage those expectations when you transfer to a CMO?

Judy Magruder
Yeah. I've seen it go both ways, to be honest with you. If you're not around while the initial plan is being developed and that timing is not included in expectations, that's a tough spot. I've been there. You go in and say exactly what you just post. So, before you make clinical material, you need to know what you have, do a little development, and make sure your methods adequately characterized the material. You want to know you can make it twice because you can go to the clinic and you can get great data, you want to be able to reproduce that stuff and use it again. Explain it that way.

I've had the head of a company say, "You know what? That sounds great, but we're going with what we have because I promised my investors I'd be in the clinic and I just don't have time." That's a risk. All those things about managing risk, and they went against the advice of the CMC person, and I'm the project manager. He's like, "Okay, thanks for your input but no." I got other companies who have a different experience, or less

indifferent, understand and say they're not willing to take that risk of heading into the clinic without a little bit more robust dataset and confidence so they could repeat making that product.

I've seen it go both ways, and I think it comes down to the decision-making from a business perspective. Can they afford it? Did they believe you? All before that time slips. I've seen it go both ways, and I don't think you can guarantee that approach will work.

Brian
No, and I don't it's not unrecoverable. I mean you can go back, you can further develop, you can under change control, you can still move things along, but you're right, it's that risk. We tell our clients to pay attention to those methods and how they're qualified because an inconsistent method can set you back in time and money like most folks wouldn't believe. Those are things that we try to insist, that there's some sort of concessions made for method development. You don't need a lot of material, but to qualify and better understand those methods, it's essential.

Judy Magruder
That is a great point, it doesn't sound exciting, but that's one of the places where risks may not be worth taking. I think, as a CMC expert, when you point and say, "Here is how I assess the risk." I mean, that's incredibly valuable for these early-stage companies, because that's what they wouldn't necessarily know. But from a CMC perspective, there are some risks you could advise by saying you can make that up later. But some risks are tough to make up later. I think that's where the benefit comes in, like the kind of advice that you've just described.

Ed Narke
Meranda, speaking of risks, while talking to some folks or investors that are looking for help with some of the programs, anything that you've picked up on early-stage companies just getting started? The prickly spots, what keeps them up at night, rumors that they heard, things you have to do, has there been any consistent messaging or questions around certain risks?

Meranda Parascandola
Not necessarily specific questions. I've had a lot of folks come to us in the earlier stage and said, "What do I have to do to make CMC work?" It's like that's a loaded question. At that point, you have to step back and educate them on how somebody can help them, guide them through those processes, because if that's their only question, they got a long road ahead of them. A lot of the earlier stage companies that we speak with, we try to guide them towards best practices or some resources that could help them think about where they need to go from here. I'm not sure, Brian, have you had any recent questions?

Brian Lihou
No, I think the one overarching theme is that there's more than one way to get there. I think early on in the pre-clinical, at least in our experience with clients who have a strong personality and they've gotten the company so far, you have to give credit where credit it is due. I think it's explaining that we on the CMC side are not inflexible either, we need to be able to be creative to find the means to an end. If anything, from what I have listened to so far, it just validates the fact that there has to be more than one way to get there. Especially in the early phase work. If you can do that with some of these clients, it shows in good faith, a willingness to work with them, and understand why they're pushing something one way and what we can do about it. To me, I think flexibility is the key here.

Ed Narke
Actually, that's a great point, you brought up, Judy, about risk. Any time we do anything in this industry and

make decisions, there's a risk involved. First of all, we base a lot of our decisions based on our experiences and the mistakes that we made in the past.

We covered a couple of things today, which was great. How to stay on track, how to be flexible, how often you should pivot, and in certain instances why, and how to effectively communicate with a team. In overarching, the bottom line is communications. If you have that, usually you have a pretty good plan and you can execute it.

I have two more questions, one of them is regulatory challenges, CMC regulatory challenges, early-stage companies, or even investors, who may have done something with a larger budget at a larger company, and they can sort of predict or tell you how things are going to work. But you know, for sure, based on the situation, it's not going to work like that. Can you give us an example, or just a recent funny, not funny, or fun experience with a small emerging group, the success story part of it?

Judy Magruder
Yeah. Sometimes you do get surprised on the upside, on the regulatory piece, believe it or not. I worked with an early-stage company that acquired an asset that had been in the clinic previously, but they didn't have a lot of the early data. So, when you pick up an asset, sometimes there's a lot of information, sometimes a lot of it has been lost. In this case, a lot of it had been lost. In their initial discussions with FDA, they said, “let's do a pre-IND meeting,” you've seen the molecule before the IND was withdrawn, but now, it's new. The company made a pitch for what I thought was a pretty skimpy IND package, given that there wasn't a lot of information in writing. Which is typically what you need to submit, you need some to submit data. The FDA was willing to work with the company. The molecules are relatively safe, at least from the data that they had. The FDA was pretty flexible on, “you can submit your IND. You don't have to have made your clinical batch when you submit the IND. You don't need to send as much stability, just give us the C of A before you dose your first certificate of analysis on the clinical batch before you dose your first patient, and we're good.”

I was shocked, to be honest with you. Sometimes, you get shocked on the good side that the FDA felt there was sufficient evidence, and I had never seen that kind of package be accepted before, but sometimes it works. I guess that goes to; sometimes it's worth asking. If you think it's safe, of course, none of us want to do anything that we think isn't scientifically sound, but if you think it's reasonable and it's a reasonable risk and the safety is there, it doesn't hurt to ask. I learned that from that experience, because previously I'd be like, "No, here's an IND package, here's what you have to submit, don't even think about asking, because you'll look bad. The FDA will think you're silly." Well, sometimes you have to rethink it and it's worth asking.

Ed Narke
Yeah, right. It goes up against what we just talked about, communications and transparency. It sounds like you can be successful and working in a partnership with agencies and data sometimes helps too. We'll throw that in just in case. Okay. Brian and Meranda, anything else here? Otherwise, I have one last question before we go.

Brian Lihou
I have one, and my question is for Judy. When is it time to plan? Is it ever too early? I know that sounds like a silly question, but we do get push back from clients, "Do we need all of this right now? All I want is X. Why do I need to have a plan?" People look at that as upselling, when it's not, because that plan can save you. At what point do you usually recommend to these small emerging companies when a plan like this is appropriate?

Judy Magruder
Day negative one. You can't go from A to B unless you know the path. If a company says, "I need to dose the first patient in eight months." Then I have a plan, "Well, okay. Let's talk about that. How are you going to get there?" It's like anything in life. Unless you have a plan, there's no guarantee you're going to get there. If you want to leave a probability that you're going to succeed, you need a plan that shows how you're going to get there. This allows you to monitor, change, and adapt along the way to assure that you're going to get there. So, yeah. Day negative one, plan.

"It's like anything in life. Unless you have a plan, there's no guarantee you're going to get there. If you want to increase the probability that you're going to succeed, you need a plan that shows how you're going to get there."

Brian
I'm going to have to borrow that because that was really well put. Thank you.

Ed Narke
Alright, the last question. Just some background here, I met Judy about seven years ago. We were at a JP Morgan conference with Dan Torok, one of our colleagues here. Somehow, we ended up working with you at a different company and – Actually, we wound up at a Starbucks, in one of those towns out there, and we started talking about what we do outside of this day job type of stuff. I found out that Judy is an avid horse rider, and at that time, my wife had a horse, was riding the horse, and I was paying for the horse, of course. I guess my last question is, how are the horses?

Judy Magruder
The horses are great. The horses are terrific. I tell people it's like, the cheapest therapist you'll ever have because when you get on that horse, everything else goes out of your head. When people talk about focus and about living in the moment, you better live in the moment, or it's not very safe. [chuckle] So, it's a great lifestyle, I don't even call it a hobby and it keeps me sane.

Ed Narke
So with that, I'd like to thank you, Judy. Judy Magruder, live from Mountain View, California. Early-stage product expert champion, horse owner, and again an all-around fantastic person. Thank you again, Judy.

Judy Magruder
Thank you, it's been a pleasure. Have a good day.

FDA CMC regulations and guidance 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.