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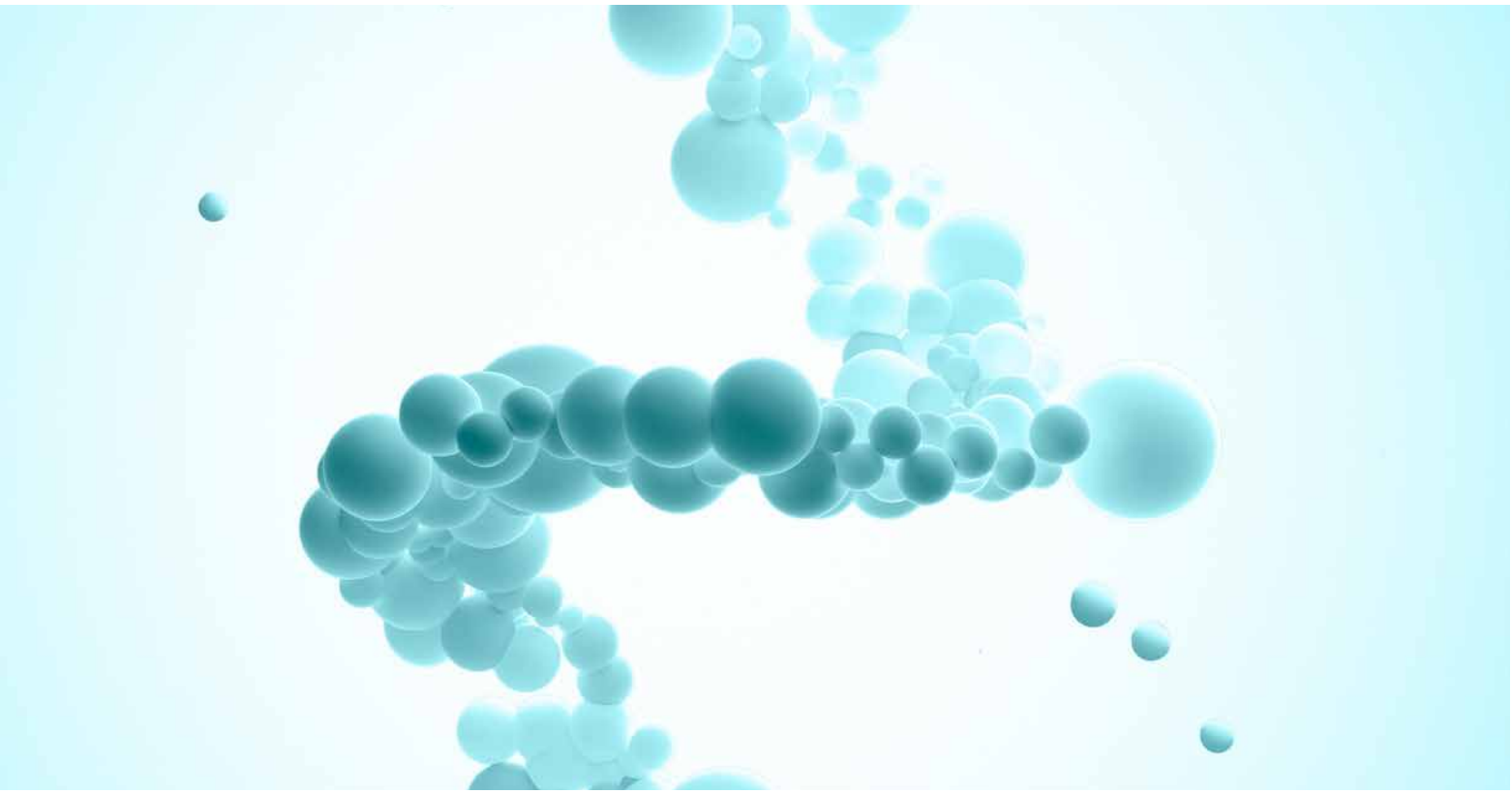

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Q&A: BIO EXPERTS

Post-discovery priorities:

Streamlining your molecule's route to IND

Ruby Casareno, PhD
Senior Vice President of Technical Operations at Allakos, Inc.

John Foy
Vice President of Business Management at Thermo Fisher Scientific

Jonathan Zmuda, PhD
Director of Cell Biology at Thermo Fisher Scientific

Senior Director
of Manufacturing at Biopharma company

Introduction

Time to market is paramount for many companies starting to consider post-discovery development and strategic plans for bringing a molecule into clinical trials and beyond. Strategies and tactics for shortening timelines often involve trade-offs related to risk and future needs, making early-phase decision-making a balancing act for even the most promising molecules.

A panel discussion hosted in June by BIO Digital 2021 brought together four experts in post-discovery strategy to answer questions about critical considerations that impact timelines and commercialization and to share insights related to methodologies, robust platform process design, high-throughput automation technologies, optimized workflows, and life-cycle approaches. The panel was moderated by Sue Behrens, PhD, Rathmann Professor in Bioprocessing and Director of the Amgen Bioprocessing Center at the Keck Graduate Institute. The panelists' responses to key questions about getting to first-in-human studies while establishing a strong foundation for future scale-up and commercialization are shared here.*

*Panelist responses have been edited for clarity and brevity.

What are the most important considerations when looking to scale up to first-in-human trials from discovery? Are these factors universally true, or are they dependent on molecule class or nature of the company, etc.?

Zmuda:

With transient protein expression systems, we put a lot of thought into which systems to use to get the necessary protein and protein quality very early on in the discovery process—when you may be looking at multiple gene candidates or high-throughput screening to identify your first candidates. In recent years, we've seen an emphasis on biologics development, CHO-based transient systems, and 293-based transient systems; CHO is certainly the most popular for development of monoclonal antibodies. This is done with the intent that any changes moving from transient CHO to stable CHO represent the minimal risks, going from one cell type to the production cell line. That said, 293 cells are still a workhorse for candidate screening. They provide a lot of protein very quickly, for example, and have more human-based post-translational modifications.

Early on, companies need to ensure the supply of protein they need in order to do all of the preclinical work *and* generate early research standard materials as well as critical reagents for all assays that will be developed. Certainly, transient systems that are able to express higher levels of protein allow you to push further to the right in the developmental process and, in some instances, even generate sufficient protein to begin work on analytical characterization and/or method development.

Senior Director:

We are working hard to move that transition from research into development and make sure the molecules we are working on in research are in fact manufacturable—that there are no molecular weaknesses that would cause a problem. We integrate activities very closely with the research group to smooth the path. And we rely on those early materials for our research reference standards and the first analytical look.

Once we get into development, scale-up for me means scaling up cell culture—the most sensitive part of the process. As soon as we get into pilot scale, the more comfortable I feel scaling up for IND. When you do contract manufacturing, you often end up with slightly higher scale-up than when you work exclusively in-house because there is limited production time if you are outsourcing the process.

We are focused on antibodies, but even the standard antibodies aren't standard anymore—we see a lot of fusion proteins, Fab [fragment antigen binding] fragments, and other fragments—the field is rapidly changing. People are deciding early on what they need a molecule to do. Do they need the antibody to have ADCC [antibody-dependent cell-mediated cytotoxicity] or do they just want it as a binder? Nowadays, a lot more is going into the design.

Casareno:

From the development space, one thing we pay particular attention to is whether your construct is going to have the mechanism of action. If it's ADCC, there are limited options for making recombinant antibodies in the industry. Only certain CDMOs [contract development and manufacturing organizations] can offer that expression system. Technical issues such as this should be part of the CDMO selection process.

Exposure to risk and risk tolerance should also be factored into CDMO selection. At most smaller companies I have worked for, I was fortunate that they paid attention to the entire lifecycle of the program—not just a fast IND. They looked carefully at the capabilities of the CDMO in case we needed to do Phase 3 commercialization with them. For these reasons, we built the following into screening of a CMDO: consideration of their reputation in the industry, their quality, and their scale out capabilities. In terms of the IND, we do want to minimize time to get to the clinic and get the proof of concept quickly. But in developing the process, we need to pay particular attention to make sure the cell line is stable, so that we can move forward with that cell line to Phase I, II, III, and commercial if needed. We

would also pay attention to formulations. You want to make it commercializable so that you don't have to keep updating it as you advance. However, in terms of the process—the upstream and downstream—having a decent process for Phase I alone is fine. We know we will devote resources between Phase II and III to optimize the process.

In the past, the industry has generally considered timelines of 16 – 22 months to go from discovery to IND acceptable. Is this still the case, or has the pandemic changed the industry mindset towards those timelines?

Foy:

Even pre-pandemic, that timeline was under pressure, and now the interest in getting into the clinic first has increased that pressure, which is reflected in customer expectations. At Thermo Fisher, we have worked over the last couple of years to establish a package that we call Quick to Clinic, designed around a 12-month timeline to IND. We feel it is becoming more of an expectation to beat 16–22 months. Of course, there are trade-offs in business risk and technology risk that we need to address in that timeline, but this is the direction the industry is going.

Part of what we built into the approach with Quick to Clinic is using cell lines from the transient expression space. We have the ability to bridge from the transient space to the stable production space to hopefully de-risk what the customer is looking for in the IND space. The pressure to reduce timelines is natural in this industry. When you factor in the pandemic over the past year, we've seen some amazing successes with timelines in the development of technology and products that were previously unproven. I think that will put further pressure on development timelines moving forward. Regulatory requirements haven't changed, of course, but the solutions to accelerate timelines have changed in the past year. Time will tell how successful these are. Some have received big press, but there have also been some treatments and vaccines in the pandemic space that were not successful. After reviewing some of that, we'll find out if that was due to how CMC [chemistry, manufacturing, and controls] approaches were used and whether the less successful outcomes involved taking too much risk in the development of some of these treatments.

Senior Director:

I agree there is an awful lot of pressure on the timeline, and I think that as a CMC professional it is something we worry about as well. Sometimes cutting a corner in cell line development can cost a lot of time later on, so it's important to understand what can be shortened. To accelerate timelines, one idea is to take a number of clones through process development while simultaneously doing stability studies, using iterative processes to speed things up.

What trade-offs could be considered during an accelerated early development timeline? And how do you effectively balance speed and risk?

Senior Director:

Emphasizing cell line and formulation development, as noted earlier, is an example. Maybe you accept some trade-offs in process development, perhaps using platform process development and applying specifications appropriate to Phase I as the priority. For example, maybe your host cell protein numbers are not as low as they will be later, but that's a temporary, early-phase trade-off that you can live with.

Foy:

This is a common conversation we have with customers: trading off the best timeline with a lower-risk approach but a higher probability of success. We look at product quality and the analytics needed to understand what's required. We build more time in. With a higher-risk approach, you may have less information about the product as you scale for the GMP [good manufacturing practices] process.

In the cell development space, there are opportunities for sure. You can consider how many clones to take forward into process development or how much data you will wait to see before moving from cell line development into a process development. You must consider cell line stability and the number of generations you want to run before moving into the pure development and GMP space. There are opportunities to manage risk *and* timelines. As mentioned earlier, it's important to understand what you can scale when you are working with a CDMO, and whether you know what your total requirements are going to be to enable clinical trials. Are we planning the right volume of product to support the IND *and* the additional work that may be needed around stability studies and the overall CMC?

What strategies can you adopt in research and development to minimize repetition of work when initiating cell line and process development?

Casareno:

We engage with the research team earlier, at the point when they are humanizing final clones. That's when we want to start that dialogue with them. The benefit is that we can do a manufacturability assessment earlier and in collaboration with them, because they would be doing the initial production of their reagents and of the clone. We would like to know the specific characteristics of this final clone ahead of time. We want the pI (isoelectric point) information and the gene sequence so that we can put it into a program that will give us all the different hotspots for aggregation, post-translational modification, etc. The other thing that helps when we're in collaboration with research is sharing with them the platform process we would use in development and encouraging them to purify the initial supply of material, then use the material to do pre-formulation screening studies. Then we could highlight the risks and stability concerns that we should pay attention to as we develop the purification process, for example. Those steps would help speed up the development process and foster a collaborative, engaging environment between research and the development group.

Zmuda:

From the standpoint of early discovery, you de-risk the process as much as possible by making your transient protein in the same cell line as your stable protein. For instance, there are numerous publications and presentations in which transient CHO cells are used as a sort of "canary in the coal mine" for their stable counterparts, or as an opportunity to look at, for example, screening peptide signal sequences in the transient setting before going into stable vector and stable cell line production. By no means would we say that this approach is 100% predictive, but certainly it gives an indication of potential problems that you may run into when moving into your stable production system.

Historically, CHO cells and the transient setting had not been able to produce the levels of proteins that were required for doing a lot of these quality studies, so 293 or even insect cells were used in their place for some early productions. Now, with the advent of transient CHO systems that can reach gram or multiple grams-per-liter levels, they are a more relevant model early on for that transition from transient to stable production systems.

In addition, researchers have an insatiable appetite for protein early on. The more you can make quickly and flexibly in a transient system, the more that you can provide to them, and the more they will run experiments, characterizations, and analytics. That allows them to have a better understanding of their molecule. Nobody likes surprises along the way. In terms of developability and generating reagents for use, consistency of the protein that you're making before you get into your stables is important. Previously, to get a gram of a recombinant protein in CHO cells, you had to run as many as a thousand reactions to get one milligram per liter of protein. But that paradigm has shifted, and we can now make grams of material in a transient setting within a week to two weeks. That allows for de-risking and having additional characterization of your molecules done early and ahead of time. While that's not a perfect correlate, the ability to work in one cell line from start to finish has its advantages in terms of reducing risk and surprises along the way.

How should you plan your early development activities to position yourself for a quick transition to scale up to late-phase clinical trials and commercialization?

Senior Director:

In the context of outsourcing your molecule, it's important to design the program and to clearly define your entire statement of work, including all of the deliverables. When you're developing in-house, you have the ability to move from one learning to the next, but when you're working with an outsourced contractor, it's important for them to plan their resources. This is universal and somewhat obvious, but I think it's important to try and sit down and think about your entire program and everything you need, including all of the development work and all of the analytics that you're going to need. Spell that out ahead of time. In the long run that's really going to help your program.

Another thing that is going to help is being familiar with the IND and the BLA [biologics license application] sections. You have to know where you're going with your information to be able to address those. Always keep in mind those sections and what they're going to be asking for, and bring that back into the design of your batch records and the design of your process.

Casareno:

Based on what we are going through at Allakos as we build our pipeline projects, defining the scope of work and the resources it will entail is a priority. We went through this first thinking we would develop the process in-house. As we engaged and screened CDMOs, we shared with them that we were considering a hybrid approach of developing the process in-house then transferring it back to their facilities. I was shocked to hear that taking that approach actually costs a lot more and takes more time. So we did an internal realignment and asked, "What is the topmost priority for the company?" Speed to clinic was the answer, which meant we would have to make some compromises internally. At the same time, we know what our negotiables and our non-negotiables are. So even though there are 12 months, for example, to get to IND, we're comfortable with a little longer timeline provided we are more involved in the evolution and the development of the process.

This space has evolved so much, but on top of knowing our scope and goals, as we go through CDMO partner selection for a fast IND, we're already asking them: "What's your commercialization experience? What is your capacity for commercialization? And if we need to go to a large scale, what is in your network?" With really good clinical data, it takes 3 to 4 years to do tech transfer and to get the process validated. For us, that's all built in as part of the IND phase for CDMO selection. That's how far ahead we are planning.

Foy:

Regarding the challenge of keeping the development of manufacturing within the CDMO or taking in a customer's process, that's one of the key trade-offs in the construct of Quick to Clinic programs like ours at Thermo Fisher. In order to get that 12-month timeframe, we have assumed that we are going to be working within our platform. We can stage our documentation and some of the raw materials and have things set up in a way that uses our process and existing operating standards to achieve that very aggressive timeline. It goes back to some of the discussion around trade-offs. If we're bringing in someone else's process and those operating conditions, we need a little bit more time to look at how we do those processes in our facilities. But yes, over the last 20 years that has evolved a lot. There are these different approaches, but in the Quick to Clinic approach we want to run with a standardized set of practices starting from that cell line that we've defined and then moving on as quickly as possible. That does take away some flexibility of the customer having input into the process design. So that's something that we need to be aware of. We still do a transfer for a number of customers that have developed their cell line or their process elsewhere, but the timeline will depend on the condition of the process when we receive it.

Understanding the full timeline of CMC development and the time it takes to get to commercialization will dictate how much work you put in pre-IND or post-IND. If the focus is really on getting to the IND and getting that first-in-human

study done, how quickly after that are you going to expect a resupply batch? Or do you expect to then do optimization because you want to move quickly into commercialization? Every customer and product has a slightly different scenario. We need to be able to understand that holistic view so that when we're looking at the immediate need versus future need, we can at least start to pencil in some of those future needs and decide if we should design in some process optimization or additional scale-up immediately after the IND to enable manufacturing. We want to start that discussion pretty quickly so that we can reserve the space and the resources to get those additional optimization activities completed.

Are there any trends or specific concerns you have encountered in your experiences getting to IND that are related to the type of product or molecule?

Foy:

A lot of what we've been talking about has focused on CHO cell-derived antibodies. There is quite a bit of knowledge in that space as far as what a "typical" development program for an IgG1 antibody should look like, although there's no truly typical development program.

We have started to see more interest in the more complicated fusion proteins and biospecifics, and it's a little bit harder to standardize some of the practices and processes around what those different molecules look like. That is now something we are looking at: How do we establish a platform in our facilities and our development labs that we can adapt to other types of molecule classes? Investing time and money in these platforms and standardized processes for alternative molecules and products will be a priority over the coming years.

What other advice do you have about lifecycle and eco-system solutions to help our audience move their products through development more quickly or get solutions to patients faster?

Senior Director:

I recommend working with research as you go through the transition to smooth the process. We've actually tried to harmonize on a generic formulation buffer that we can typically use. I also suggest getting early input from your clinical operations group. Do they see this being a high-dose molecule? Likewise, get input from your regulatory group. Is this an orphan drug? Knowing these sorts of things can help position and guide you in terms of what you want to make, how much you want to make, and how you want to make it.

Casareno:

One thing that would be great to shepherd a program from gene to IND is having a defined CMC governance structure within the company. When you have an external collaboration with your CDMO, it's project manager [PM]-driven. I think it's important that internally you have a concrete organizational structure that could interface with the drug substance facility as well as the drug product fill facility. Some CDMOs are one-stop shops with one PM for both and that really helps drive the timeline to IND even faster. Clearly defined roles will really help for your process lead, technical, quality assurance, and regulatory leads, making sure it's a cross-functional team making all of those important manufacturing decisions.

Learn more about accelerating your post-discovery development timeline to get life-changing, high-quality therapies to patients as quickly as possible.

Panelist Biographies

Sue Behrens, Moderator

Rathmann Professor in Bioprocessing and Director of The Amgen Bioprocessing Center – Keck Graduate Institute

Dr. Behrens joined the Keck Graduate Institute as the George B. and Joy Rathmann Professor in Bioprocessing and Director of the Amgen Bioprocessing Center in 2019. Prior to this, Dr. Behrens served as the Senior Director for Process Engineering at Integrated Project Solutions (IPS) in Blue Bell, PA. Within that role, she developed innovative and cost-effective solutions for complex research and manufacturing facilities within the life sciences industry.

Before IPS, Dr. Behrens held progressive leadership positions with Merck & Co., Inc. for 20 years. Starting her career in technical operations supporting large-scale fermentation operations, she held positions in research and development and capital team leadership. Subsequently, she oversaw sterile process technology and engineering functions at Merck's largest site, including the launch of four new products. She also led Merck-Schering Plough's biologics science integration efforts. Ultimately, as Senior Director, Biologics Manufacturing Science & Commercialization, Dr. Behrens provided biologics manufacturing technology leadership at multiple development and manufacturing sites worldwide.

Ruby Casareno, PhD, Panelist

Senior Vice President, Technical Operations – Allakos Inc.

Dr. Casareno has more than 17 years of biopharmaceutical experience in biologics process development, scale up, technology transfer, and contract manufacturing oversight. She contributed to 3 commercial and more than 18 preclinical and clinical development programs. She was Director, Outsourced Manufacturing & Manufacturing Sciences and Technology at Portola Pharmaceuticals and led the biologics team in addressing BLA drug substance manufacturing-related regulatory questions.

As Director of Process Development and Manufacturing at Oncomed Pharmaceuticals, Dr. Casareno was responsible for biologics process development and ensuring GMP adherence for 9 clinical development programs. She held various scientific and leadership positions at Seattle Genetics, Maxygen, Johnson and Johnson (Scios), Xoma and Bio-Rad Laboratories.

John Foy, Panelist

Senior Vice President, Commercial Operations – Thermo Fisher Scientific

John Foy is the Vice President of Commercial Operations for Thermo Fisher Scientific's biologics CDMO team. John is a senior leader with over 20 years of experience in biologics CDMO services holding roles in business development, operations, and program management. He earned a Bachelor's degree in Mechanical Engineering from Lehigh University and an MBA at the University of North Carolina at Greensboro. John started his professional career with four years in the United States Air Force.

Jonathan Zmuda, PhD, Panelist

Director, Cell Biology – Thermo Fisher Scientific

Dr. Zmuda is the Associate Director of Cell Biology in Life Sciences Solutions at Thermo Fisher Scientific, Inc. Prominent among his roles, he leads a team dedicated to discovering and developing new technologies and products useful for cell biology applications, including protein expression, cell culture, rare cell analysis and instrumentation.

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+1 919 226 3200 • thermofisher.com/patheon • pharmaservices@thermofisher.com

Published 10/21

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