EP.163 – Frank Gupton

Narrator: You're listening to *BioTalk* with Rich Bendis, the only podcast focused on the BioHealth Capital Region. Each episode, we'll talk to leaders in the industry to break down the biggest topics happening today in BioHealth.

Rich Bendis: Hi, this is Rich Bendis, your host of *BioTalk*. This is our first *BioTalk* since we had our first BioHealth Capital Region forum late in September, and we have a guest that actually was one of our speakers there and someone we've been interacting with over the last couple years as the BioHealth Capital Region has gone south a lot more to partner with our friends in Virginia. Dr. Frank Gupton is one of our friends in Virginia that we're partnering with, and he has a lot to talk about how we can work together and grow the BHCR even more. Frank, welcome to *BioTalk*.

0:00:59

Frank Gupton: Thanks, Rich, very much for the opportunity to share my thoughts with you on all the stuff that's going on down here in the capital city.

Rich Bendis: That's super. The other thing is that Frank has actually got so many titles. There's a couple I'll give you, but he's going to go through all of them with you when he does his self-introduction. But the ones I know best are that he's the co-founder of Phlow, and some of you probably know that Eric Edwards, who also is one of the co-founders of Phlow, is on the board of BioHealth Innovation. Frank is also the CEO for Medicines for All, and we're going to learn about Medicines for All as we've talked about that before on the *BioTalk* podcast in the past. Frank, rather than me go through some of your other chairs that you have and distinguished positions in academia, please to a self-introduction for our audience.

Frank Gupton: Thanks, Rich. I'm the chair of the Chemical Life Science Engineering Department at the College of Engineering at VCU, and I'm also the Floyd Gottwald Endowed Chair of Pharmaceutical Engineering in addition to being the co-founder of Phlow and the head of the Medicines for All Institute.

0:02:00

Rich Bendis: Excellent. Talk a little bit about your career and how you evolved to get into this academic role, because I don't think you started in academia.

Frank Gupton: No, I didn't. I'm clearly a nontraditional academic, Rich, and yes, the thing I think about is everything kind of had to happen the way it did for me to be doing what I'm doing here today. I started out my career at Commodity Chemicals out of graduate school, worked for a large chemical company, Celanese—and they ended up getting acquired by this really large chemical company, Hoechst; it was a German chemical company at the time—and had the opportunity at the time to work on processes that were more continuous in nature because the margins were typically tight on these products. That kind of gave me a starting point to look at how we could actually produce drugs that were more effective. I was involved in the ag chemical business and made intermediates for a company called American Cyanamid that had some great herbicide products, and we developed processes to make some of the key building blocks for that.

0:03:03 Then we made intermediates for the pharma sector, and then went ahead and started working on active ingredients. I guess I was there for about 16 years, and then I was approached by the folks at Boehringer Ingelheim Pharmaceuticals to head up a North American process development group in Virginia. I joined that group in 1993 and was there until 2008. Then I retired, and I was happily retired.

I had been on the advisory board of the engineering school of VCU for a while, and the dean of the humanities and sciences and the dean of the engineering school got together and approached me with the idea of taking a joint appointment between chemistry and chemical engineering. I'm an organic chemist, but my research groups were typically a 50/50 mix of chemists and chemical engineers, so to this day I swear my wife called them and told them to get me out of the house. She talked me into it. She said, "You know, you just do a little bit of research and teach a course or two."

0:04:00 It evolved into something much bigger. I started doing research here in 2008, and we have a huge research footprint now as a result of a lot of the great people that we've been working with.

Rich Bendis: That's really a diverse and interesting background, and some of that I have some relationship to because I didn't know a lot about your background, but Hoechst—basically, I used to be with Marion Laboratories.

Frank Gupton: Oh, up in New Jersey?

Rich Bendis: Well, no, in Kansas City. I still have a home in Kansas City, and that's where Marion's headquarters were with Ewing Kauffman, and then Hoechst actually got involved in that acquisition. Marion went through many acquisitions and became Marion Merrell Dow, then Hoechst Marion Roussel. So anyway, I know it from that. And then being in Pittsburgh, I knew American Cyanamid because, I don't know if that was their headquarters, but they had a major facility in Pittsburgh.

Frank Gupton: Yeah, they had one in Pittsburgh. They had one just outside of Saint Louis, but their headquarters was in New Jersey.

0:04:56

Rich Bendis: Oh, in New Jersey. Okay, gotcha. Yeah, so anyway, we're one degree separated on a couple counts there, Frank. Before we get into some of the academic things and the chairs you're in, I think the things that we have interacted with most and have had a lot of attention over the last couple years have been both Phlow and Medicines for All, so if you don't mind, give us a little background on Phlow first, and then we'll go into Medicines for All afterwards, because both of them have pretty much a significant role that they're playing, not just locally or regionally, but also nationally at this point.

Frank Gupton: It might be of value to the audience to start with how Medicines for All got started, because if Medicines for All hadn't been in place, we probably never would have gotten a call from the federal government. One of the last things I did when I was in industry was to develop a process for an HIV drug Nevirapine, and it turned out to be used in all the combination drug therapies at the time.

0:05:57 I'd been at VCU maybe a year or two, and the Gates Foundation found out through a series of different informal conversations that I was here at

VCU. They approached me with the idea of looking at Nevirapine, having had that insight into where the opportunities are in the process, to figure out if we could reduce the cost a little bit because the volumes were really high—it was like several hundred metric tons of material that was being produced at that time. So, we looked at it, and I was a little concerned when they asked me to look at it because I felt like we had a pretty good process when I left industry. But we came up with some new chemistry, and they gave us $5 million to look at reducing the cost 10 percent, and we reduce the cost 40 percent. But in addition, one of the things that we did, Rich, was we had a dramatic decrease in the carbon footprint of that process. Most pharma processes generate several hundred kilograms of organic waste per kilogram of product. This one wasn't as bad; it was about 80 kilograms, but we cut it to 4, and we won the presidential award for green chemistry that year for the work on that process.

0:07:05 Then the Gates Foundation gave us a second drug, and we had similar results with that one. Then they gave us a third drug, but then they added a comment saying, "We think you've identified some low hanging fruit, and we'd like for you to look at tuberculosis and malaria drugs too." And I said, "Well, I don't know that we can do that." And they said, "Well, what if we gave you enough money to build an institute?" And that's how Medicines for All got started.

Rich Bendis: Ah, super. What year was that, Frank? Do you remember?

Frank Gupton: 2017, I believe.

Rich Bendis: Okay, gotcha.

Frank Gupton: We got our first grant in 2014, so we got $25 million to establish the institute, and with the original result three bonuses of $5 million for the first three drugs, we were up around $40 million. So, we looked at all the first-line therapies for HIV and reduced the cost in each one of those, then we looked at tuberculosis and four new tuberculosis drugs. I don't know if you knew this or not, Rich, but there's a tuberculosis epidemic in Africa and Asia, and it's a resistant strain of TB, so they needed new drugs to be able to produce it.

0:08:05 The challenge is that they were fairly complicated molecules, and in order to get uptake in those low- and middle-income markets, the price has to be sufficiently low to penetrate the market. So, we reduced the cost of those drugs anywhere between 40 and 60 percent. So, we did that, we also did a malaria drug, and then COVID hit and we started working on COVID drugs for the Gates Foundation. We looked at the key building block from Remdesivir. Then we did a process for Molnupiravir, the Merck drug, and then lastly we started working on nirmatrelvir which is the active ingredient in Paxlovid. About the same time, the folks at Pfizer called us and said, "We're worried about the process to make the starting material," so we worked with Pfizer on developing a new process for one of the key building blocks for nirmatrelvir.

0:08:52 About that time, some colleagues of mine had made the government aware of what we were doing with the Gates Foundation, so when COVID hit, we were approached with the idea of re-onshoring pharmaceutical manufacturing back in the United States. In explaining it to folks in government, it posed the question, "What would it take to re-onshore pharmaceutical manufacturing back in the US?" And I said, "Well, it's a bigger problem than you think it is. It's not just the formulated product or even the active ingredients. All these starting materials are being made in foreign countries too, so unless you can have a holistic approach, you're always going to have a vulnerable supply chain." And they came back and said, "Okay, we'll get back to you." And then when COVID started to accelerate, they called us back and said, "We need to do something like right now." So, my colleague Eric Edwards and I formed this company, Phlow Corporation, and I had a colleague of mine who was the CEO at the time of AMPAC Fine Chemicals which had acquired the old Boehringer Ingelheim site that I was very familiar with, and it was relatively empty, and it was on about 300 acres.

0:09:58 So, we approached AMPAC with the idea, and we brought the folks in the federal government down, and we also brought our colleagues from Civica who we'd been discussing the prospect of how we might be able to work with them too on sourcing the active ingredients. The idea was: Could we put all three of those capabilities on one site here in the United States? So, AMPAC making the starting materials, Phlow making the

active ingredients, and Civica making the formulated product. The federal government gave us about $360 million to get started, and I think we're up about $500 million right now with regards to all the additional work that's been done, and we're getting ready to put out our first drug very shortly out of Phlow.

Rich Bendis: Congratulations. That's a really interesting backstory on how you got involved in Phlow and what you're trying to do to solve a major problem in America that we have, and in advance, hopefully, of any future pandemics or other crises that we might have, because we want to have a little more control of our own supply chain in the future, which I know that that's been a challenge.

0:11:03 You say you're getting ready to launch or get ready for your first drug, so tell me a little bit about how you prioritize what you're going to work on. I don't know if you can talk about it yet, but if you can, talk about the first drug that you're getting ready to release. And what does "release" mean?

Frank Gupton: Yeah, so we'll release the active ingredient that was our charge at Phlow. What was funny when we first started doing this, there was a lot of discussion about which drugs are essential medicines and how to prioritize them, and one of the things we found out was that there was one drug—and I'm not sure if I'm allowed to talk about it—but it was used to intubate patients, and it had gone into short supply, and it was used in a lot of other applications. What was really interesting was that the company that was making it couldn't make it cost effectively, so they exited the market. So, we developed a new process of Medicines for All to be able to make it more cost effectively. We transferred that over to the folks that Phlow, and they're scaling that process up as we speak.

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Rich Bendis: When you say they went out of the market, does that mean that you acquired the rights to the technology? How did you get involved in that?

Frank Gupton: It was a generic drug, so there was no IP around it, and we developed an entirely new process to make it, so we had our own IP.

Rich Bendis: Excellent, thank you. So, that's the first, and then how many more do you

believe are down the road? And how many more hundreds of millions of dollars is it going to take to get them out the door?

Frank Gupton: I think the hard part was actually building the asset from the ground up, and that takes some time. You also have to get FDA approval on the facilities and everything, and staff it properly. It's been quite a challenge, but I think that the company has come up fairly quickly on the learning curve, and I feel very strongly that we'll be in position, now that we have that institutional knowledge, to be able to make these things much more efficiently than maybe out the gate, particularly when we're building the railroad while we're running the train down the track.

0:13:07

Rich Bendis: Got it. Well, Phlow is a unique entity. The question is: Has the government recognized that they might need to have multiple Phlows around the United States, or is Phlow basically in the position to sort of lead this whole initiative nationally?

Frank Gupton: It's kind of a two-part question. When I start looking at where Phlow is headed, I think they're the black swan: until you see a black swan, they don't exist. So, I think if we're successful—and I'm assuming we'll be successful; we're in a good position to be successful—that it could be a template for expansion of Phlow and/or others. Because the other thing that we're working on, Rich, is kind of an international approach to process development at Medicines for All, so another project that we're working on is a tuberculosis drug that is kind of the gold standard for treating this resistant strain of TB.

0:14:03 It was pulled from the market because it had nitrosamines in it, so we developed a nitrosamine-free process to make that, and we did it continuously. And now we're transferring that process to Africa, and it'll be the first active ingredient produced on the African continent, and it'll be done continuously. And I think about it from the perspective of an extension of the question you had. The analogy I make to what we're doing right now in the pharmaceutical sector is pretty similar to what went on in the cellular-telephone sector back in the '90s. The United States was a late adapter because we had legacy investments in hardware

systems, and places like India and China could make a step change in communications technology. We're in a situation now where we have that same opportunity here in the United States and in Africa because we have a clean slate: we don't have a whole lot of manufacturing here, so we can actually use the best technology possible.

0:15:00 Because when you start looking at the root cause of why people, why organizations left the United States, it was mainly driven by the fact that these batch processes that were being widely used in the pharmaceutical sector were very labor intensive. So, pharma companies being smart businessmen said, "Let's go to the places where the labor costs are the lowest," and that's India and China. And now you're in a situation where if you use new technology, now you can start to create a more level playing field, because if you automate and develop continuous systems, your labor costs are going to go down, and that will allow you then to be globally competitive with regards to other manufacturing platforms around the world.

Rich Bendis: What's really interesting is what you're doing in the US, being helping emerging countries which is where a lot of the problems lay. I'm going to ask you maybe more details than a typical person would ask you, but in order to go to Africa, it's not easy.

0:16:00 So, the question becomes: Does Medicines for All and Phlow set up operations over there? Do you develop partnerships with other people who are already in Africa? Or, how do you plan to enter that market, keep the cost down low, and make sure you ensure the quality over there?

Frank Gupton: If you start looking at why we've been successful, Rich, it's because we talk to people. Pretty simple. Before Phlow ever got started, I was giving a talk in Johannesburg, South Africa, and there was a gentleman in the audience, and he said, "You know, Dr. Gupton, we've got a facility we built here for animal health drugs, and we'd really like to be able to manufacture drugs for human consumption." And it isn't much difference in FDA requirements for the two. And he said, "Can you stay an extra day and come visit our site?" So, I stayed an extra day. I went over there, and they had a really world-class operation. I was really impressed. And they said, "We've got a question for you. Where do we send a check for the

process that you developed for Nevirapine?"

0:17:02 And I kind of laughed, and I said, "That's a free process. The Gates Foundation gave us the money up front, and you're free to practice it." And they said, "Well, can we partner with you?" So, we've been working with them. Not only are they working on these HIV processes that we've developed, but the one that seems to be the highest priority is this other drug to treat TB, and that's the one we're working on right now, and it's a totally continuous process. So, it's going to be a really interesting step change when you start looking at going from no technology to a really automated system that's head and shoulders above what's been practiced in the marketplace so far.

Rich Bendis: I really believe Africa is an untapped market. A lot of people, as you mentioned, went to China and India, and they're still there, but I think Africa has some of the same qualities with a lot of smart people. Believe it or not, at our BioHealth Capital Region meeting that we had two or three weeks ago, there's an organization called TASK which is a CRO down in South Africa.

0:18:00 They're trying to enter the United States, but they had one of their companies present at our Crab Trap competition. So, we actually developed a small partnership with South Africa through TASK, and I don't know if you know that organization, but I'd be glad to—

Frank Gupton: I do, yeah.

Rich Bendis: Oh, okay, so it's a very small world. He came to our meeting and said, "Boy, I love this meeting. It's a little more intimate than going to Boston or San Francisco," so he liked the culture and the people that we had in the BioHealth Capital Region. He said it was easier to navigate and meet people, and everybody's willing to talk, so I'm sure when you say "communicate," I think that's one of the strengths of our region. And what you're doing down there in Virginia is you're willing to talk to people, but more importantly, you're willing to listen.

Frank Gupton: Well put. Yeah, we try to listen. We're obviously very excited about all the things that are going on here. What we really feel like, Rich, I think that when you start looking at the African opportunity, the interesting thing

about that financial model is almost all the HIV, malaria, and tuberculosis infections are centered in Africa.

0:19:05 So, basically what they've got is they've got pent up demand for these drugs, so they can actually base load facilities with this internal requirement that would allow them to operate at variable cost to export too, so they could then become what India and China were to the cellular telephone business. I'm really excited about hopefully seeing that come to fruition.

But the other thing you think about is: How do we work together to solve these more fundamental problems? Because if you took the top 100 drugs in the United States—and the reason why the TASK folks are interesting to me—about 60 percent of those drugs have a fluorine atom in them. There's only one place in the world that actually fluorine chemistry is being practiced to make these fluorinated intermediates, and that's China. I was over in Cape Town about a year and a half ago, and we were talking about how we can work together, and I mentioned this issue about fluorinated molecules, and my colleague says, "Oh, do you realize that South Africa does more fluorination chemistry than anybody in the world?" And I had no idea!

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Rich Bendis: How about that!

Frank Gupton: The question is, how do you redirect those resources to doing things where you have the supply-chain vulnerability problem?

Rich Bendis: Wow! It's amazing: You're really in the center of it, and then until you start discussing what some of the challenges are, some of the answers are sitting right in front of you, really.

Frank Gupton: The other thing that's interesting, Rich, I had a project that I was working on with the folks at MIT. The chief of the chemistry department and the chair of the chemical engineering department were working on a unit that was called Pharmacy on Demand, and it was about the size of a big refrigerator. You put the chemicals in the front end, and it formulated the product. It made the active ingredient, formulated the product, and pills

came out back. You could make about 1,000 pills of Cipro a day with this thing. My colleagues at MIT would come down here, they looked at our labs, and they said, "You know, we don't have anything like this up at MIT."

0:21:00 And I said, "Well, you know, it's kind of amazing what you can do with $40 million." [Rich laughs] And they all kind of laughed. But the next question gets back to the root issue that you brought up. They said, "Well, how did you get the money?" And I said, "Well, I realized I'm an old guy, and I'm impatient. And I realized if I compete with MIT in MIT's space, I'm going to lose. But if I create my own space and become a leader in that space, then I can win." And that's basically what we've done here in Virginia, is that we become the undeclared leader in all this new technology for producing drugs more cost effectively.

Rich Bendis: A lot of entrepreneurs can learn through this process. I'm talking to Dr. Frank Gupton who's the co-founder of Phlow and CEO of Medicines for All in Virginia, and is really identifying gaps that exist in niches that are not being fulfilled. Whether it's luck or strategy, Frank, you guys have identified some major gaps and niches where you guys can become the global—or are the global leader at this point, and can only grow from there actually.

0:22:02

Frank Gupton: Yeah, we're pretty excited about it. Because I'm a person of faith, and I really believe that I'm not that smart enough to figure out how I got here doing this stuff, that I was pushed in these directions. I mean, you look at my background—it was funny, I have a colleague of mine who's head of the Max Planck Institute in Berlin, and he invited me over to give a plenary talk. They've got this castle that they own, and they had all the people there. We had dinner together, and he turned to me and he said, "You know, Frank, I looked at your resume. You know, you really don't belong here." [Rich laughs] I said, "Peter, you're probably right, but it's great that I am, and I appreciate the opportunity to talk to your people."

Rich Bendis: Well, I'm glad he hasn't seen my resume because I don't have a PhD or a master's in anything related to life sciences or biotechnology. But here we

have two people that are bastards in our own roles, doing what we do, but hopefully making a contribution to give back right now, really.

Frank Gupton: Absolutely.

Rich Bendis: Yeah. Let's talk a little bit about structure about these organizations. We've talked about Phlow and Medicines for All. Is Medicines for All a nonprofit, Frank?

0:23:05

Frank Gupton: Medicines for All is embedded in VCU.

Rich Bendis: Okay, it's an extension of Virginia Commonwealth University.

Frank Gupton: I've got kind of one foot in the engineering school and one foot in the healthcare system too, and I'm also reporting to the vice president of research right now. So, the structure that we have is a testimony to the fact that academia really doesn't know what we are or what we do.

Rich Bendis: Well, it's amazing you've been so successful being embedded within an academic institution, but I guess they give you a lot of autonomy, as you say, because maybe they feel, "You guys are the experts, let them run with it. We can be the platform." The university can be the platform for it to be embedded. At some point, is it something that might spin out independent of VCU?

Frank Gupton: Here's the thing I would say, Rich, and this is where I think the opportunity is. Start looking at the mission of Medicines for All. The mission for us is to provide access to healthcare to everyone.

0:24:01 But equally important, it's to train that next generation of scientists for the grand challenges of the 21st century, and I don't think we're going to be able to do that outside of academia. So, the thing that I think about that really resonates with me is this hybrid system that I live in every day between the chemistry department and the chemical engineering department. When we start looking at why we've been successful, it's because the real problem is right at the interface of those two disciplines. It's not just all chemistry and it's not just all engineering; it's having that synergy between the two skill sets. So, having positions in both

departments, I have PhD students in both areas that cohabitate, and they cross-train each other. I can tell you that the biggest frustration I have right now with my research group is that pharma wants to hire our people before they finish their theses.

0:24:58 I had a couple of cases where they had to leave to take a job and then came back and finished their theses, and it was kind of painful. I'm not doing that anymore. But we had some amazing students who are now in leadership positions at Pfizer, Merck, and Biogen, all these other places that really kind of value the broader skill sets that our students bring.

And it was funny, I have a colleague of mine who used to be vice president of research at Pfizer. We were talking about students, and I asked him a question. I said, "Where do you recruit your students from?" He said, "Oh, we always recruit from MIT and Harvard." And I said, "Well, how long did it take from the time you hired them to when they became a productive asset?" And he said, "Typically about 18 months. I've talked to our people at Pfizer. The reason why they love your people is because they come to the company hitting the ground running." So, if you think about it, I had a really great boss early in my career, and he said something to me coming out of graduate school. He said, "Frank, if you'll remember two things, you'll be really successful here."

0:26:00 He said, "You're coming from academia, and in academia, elegance is complexity. In industry, elegance is simplicity. So, make sure you err on the side of simplicity, and that will really put you in a good stead here." And I think that some of the challenges when people come from some of these high powered research groups, in order to get publications, you have to work on complex problems, but when you're working in industry, it's all about getting that product to the marketplace, and that's one of the things our students do really well.

Rich Bendis: So basically you're following the KISS principle, "Keep it simple, stupid," right?

Frank Gupton: Absolutely.

Rich Bendis: Gotcha. One of the other things that you've been able to accomplish, which has been a challenge for a lot of people in private-public

partnerships, what you're doing is academia, government, and industry all trying to work together. And you've had BARDA, you've had HHS, you've had other elements of government, you've had multiple academic institutions, you've had AMPAC, Civica, Pfizer, everybody coming together. Tell us about what's worked, and what are the challenges when you're trying to put all of those partners together in doing what you're doing right now.

0:27:07

Frank Gupton: Boy, Rich, I've dreaded that question.

Rich Bendis: We saved it up for you, Frank.

Frank Gupton: I'm sure you did. Here's the thing I would say. They all present different challenges, and when you start looking at the root cause of that, it's mainly because they all have different priorities. So, when you start looking at VCU—let me start with that one. One of the major things that VCU is interested in is building a research enterprise, and one of the things that they get measured against is the research expenditures from the grant. The way these grants work is, typically—not necessary with the Gates Foundation—but typically, when an investigator gets a grant, like, say an NIH or an NSF grant, the university gets half the money approximately, but they only get it as the researcher spends the money. So, if in the first year they spend $100,000, the university gets $100,000.

0:28:00 So, this becomes a revenue-generating activity for the university, and it's a metric that everybody uses to compare programs. So, when you look at our little chemical engineering program here, we represent about 60 percent of all the research expenditures for the entire college of engineering. Plus, when you start looking at us, we're in the top five in the country of chemical engineering programs in research expenditures. This year, I think we were somewhere between $13 million and $14 million. You compare that with UVA, Virginia Tech, those two organizations were $5 [million] or less, so you can see that we really distinguished ourselves in the area of funding for research. And being associated with the Gates Foundation really does create a level of credibility with the university that you probably couldn't get from an NIH

or an NSF grant. So, that then became a really important lever for having this close collaboration with the university. They felt that they were getting something out of it, as were we.

0:29:05 So then you start looking at Phlow Corporation. The Phlow Corporation is a public-benefit corporation, so that has to have an element of profitability, but it also has to have a viable mission that you are focused on, and you can demonstrate and point to on an annual basis that you're achieving that goal. So, they have a similar role in making sure that we have access to these essential medicines—a little bit different than Medicines for All in that Medicines for All is looking at global health as opposed to domestic drugs in short supply. So, that's probably how they might focus their efforts.

Rich Bendis: Before you leave public-benefit corporations, our listeners, most of them have never heard of a public-benefit corporation. Talk very briefly in your words, what's a public-benefit corporation, profit, nonprofit? What's the difference? And why is it a public-benefit corporation versus a 501(c)(3), a C corp, or an LLC?

0:30:05

Frank Gupton: Fortunately, I'm not a lawyer, so I'm on shaky ground.

Rich Bendis: That's okay.

Frank Gupton: But what I will say is this. When we started this—our colleague at Civica is a nonprofit—and they recommended that we not be a nonprofit, particularly if we were going to be a pharmaceutical company. They said that there were so many questions that were raised about how can you be a pharmaceutical company and not be interested in profit? So, when you start looking at the mission of what we were doing, it was not solely driven on profitability but also on achieving an objective that we felt was in the best interest of the public. I think we were the first pharma public-benefit corporation that was approved by the FTC in, I think it was like 2022 or 2023. That was a different set of challenges, and I think that we continue to make sure that we blend in the mission with the profitability.

0:31:03 Because at the end of the day, Rich, if we can show that it's sustainable by

generating an income off of this that we can then plug back into the organization, then it'll demonstrate that it isn't just something that's being propped up artificially by the federal government or the state government. I think that we've been very fortunate to receive funding to provide funds to be able to support the capital investments, because I had some pretty tense discussions with the federal government about investing in Phlow, and what came out of it was they were in essence saying, "We are for free trade in the United States." And I said, "Well, so am I." And they said, "So, why did you take the money?" And I said, "It's pretty simple. Who are you competing against?" [They said,] "In foreign entities. It's these foreign pharma companies."

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I said, "No, it's more those foreign governments who are subsidizing those companies to be able to allow them to operate at variable cost so that they can undercut us in the marketplace, and what you all did was create a level playing field for us." And they immediately said, "We're on board." [Rich laughs] I think that it's understanding how we compete globally in the marketplace, and I think that that's helped a lot.

Rich Bendis: Yeah, I think ultimately—and I talk about this in nonprofits and when I'm speaking about partnerships—if you have academia, government, industry, and NGOs who are all trying to work together to solve a problem, you have to find a common mission. And what you found is a common mission, which is you want to provide medicines to all at a lower price and help improve healthcare on a global basis. That's the common mission, and if you can find a way that all four of these different things in a private-public partnership are willing to go for that mission, then they're able to modify some of their goals and the way that they manage the finances around their programs.

0:32:57

Frank Gupton: And I think you hit on something that was really important too, Rich, and that is our workforce. Obviously I was in pharma, and I enjoyed my time there, but you can go to work for pharma and it's all about your P&L at the end of the year. We get some great students and we get some great employees because they understand and embrace the mission of what we're doing, and I think that's one of the differentiators in our business

model from others.

The other thing I'll say, Rich, that's important to me is this interface with education. Because I was very fortunate—and you probably heard this story about me before—but I was not a good student in high school. I went to college on a basketball scholarship, and if I hadn't gotten a basketball scholarship I wouldn't have gone to college because my parents couldn't afford it and my grades weren't good enough. I got a D in chemistry in high school. I started out when I was in college as a physics major, and I realized that I was going to need to do a double major in math and physics. I had to take chemistry my sophomore year, and I had a wonderful teacher.

0:34:00 He was amazing. And at the end of the year he said, "How would you like to do research with me this summer?" That changed my life, because all of a sudden everything that I was learning in a classroom I could apply to a real world problem. And I think that that's one of the opportunities that we miss in academia these days. So, we incentivize all of our faculty to bring undergraduates into our program and work in the laboratory and take the things that they learn in the classroom and apply them to some of these real world fundamental problems. And it works. Over 50 percent of our graduates, anywhere between 50 to 80 percent of our students have an undergraduate research experience. To me, that's one of the reasons why I'm here is to do that kind of payback for all those times when people took a chance on me when they probably shouldn't have.

0:34:50

Rich Bendis: Well, I think we have a similar background, but what you're talking about is mentors, basically. I've been fortunate through my career and most of the stops, and especially in the early formation of my career, to have mentors in the companies that I was associated with that took an interest in me, not because I was the smartest on the block, but because I was willing to work hard and willing to learn, similar to what you're experiencing. So, the key is if you can expose these students early on in their academic career to people that can have an influence like that in their lives, it's definitely going to have a dramatic impact on where they end up with their life and their career.

Frank Gupton: It's funny that you mentioned that. I had one student that I really have been tremendously impressed with. They asked me to provide nominees for Fulbright scholarships, so I put that person up for a Fulbright scholarship not looking at the person's grade-point average at the time. I looked at it, and the person had a 4.0, and in chemical engineering that's pretty tough. So, I invited the person over to my office to talk to them to make sure they knew that they had been nominated, and I said, "Why did you pick VCU?" And the person said, "It was the *only* university that accepted me."

0:36:00 [Rich laughs] And I said, "What about our sister institutions within the state?" They said, "I got rejected from both of them." How much talent is being wasted every year, Rich, by not taking a chance on somebody? It's just crazy.

Rich Bendis: You see all these rankings—my kids have gotten me onto Instagram—and they rank the schools, and they show what the criteria is: GPA, extracurricular, your ACTs, SATs, everything else that you have to do, and it's amazing. I just saw something today related to this, Frank, and it's basically which universities put a higher weight on extracurricular activities than they do on GPAs and your standard test scores. It's interesting to see the names of those universities in there.

Frank Gupton: Well, you know what's funny, Rich? We're talking about reinventing the pharmaceutical industry, but we're also looking at how we might be able to reinvent the whole education process. I got invited by Michael Crow, who's the president of Arizona State, to come visit him and his leadership group.

0:37:02 They are turning the academic paradigm on it's head. They've got an engineering school that's as big as VCU. It's 30,000 students. They don't have any departments. They have thrust. They have energy, health, environmental, material sciences, and probably a couple of other ones, and what it does is it allows different disciplines to cohabitate to solve problems that are most likely at the interface of those disciplines, kind of like what we're doing with chemistry and chemical engineering. I was just so impressed with what they've been able to accomplish as far as changing that whole paradigm for education.

The other thing that was amazing to me was they're getting ready to start a medical school. They're doing it in conjunction with the Mayo Clinic. They're requiring all the med students to have at least a bachelor's degree in the engineering discipline. So, they're thinking differently, and I think we're almost past time for people to be thinking differently about these things.

0:38:00

Rich Bendis: Yeah, I agree. I had an opportunity to serve on the council on competitiveness board with Michael Crow, and he was really an innovative guy there. I didn't know it until today, Arizona State has 85,000 students and is the largest university in the United States. I would have never guessed that.

Frank Gupton: Yeah, it's bigger than that. It's 85,000 on campus!

Rich Bendis: Oh, on campus.

Frank Gupton: 60,000 online.

Rich Bendis: Oh my goodness! Yeah, I had no idea about that, really. Now, you were talking about manufacturing and workforce. As we start working towards the end of this podcast—and we could talk forever, and I'm talking to Dr. Frank Gupton who's the co-founder of Phlow and CEO of Medicines for All—let's talk a little bit about the future of advanced manufacturing, pharmaceutical manufacturing in the United States and globally. So, automation, AI, continuous manufacturing, all these things we're hearing right now around manufacturing are going to impact what pharmaceutical manufacturing looks like in the future. Tell us a little bit about what your vision is for the future.

0:39:01

Frank Gupton: Let me start with continuous chemical processing, and I'll kind of revert back to the beginning of our discussion, and that was my time at Celanese working in continuous processes. Continuous processing isn't new, it's just new to the pharmaceutical sector. So, I think the good news is it's not like you're having to come up that far on the learning curve.

The other thing that I think that's really important is if we're going to bring this pharmaceutical manufacturing capability back to the US, we can't do it in the way that it's been done in the past because, not only this issue about cost, but our carbon footprint. Most of these processes generate huge amounts of waste. Nobody's going to accept that coming back into the United States, so we need to make sure that we reinvent the chemistry as well as the manufacturing platforms to make sure that they address both of those issues, both cost and environmental impact.

The thing I think about that is a real opportunity and low hanging fruit is: How do you get people thinking differently about how to put molecules together that are fairly complex in the pharmaceutical sector?

0:40:06 The thing I talked about with one of my colleagues from MIT is that, I said, "You know, we really misnamed this. We shouldn't have called it flow chemistry, what we should have called it is kinetic chemistry," because if we did that—if you look at a round-bottom flask or a big batch reactor, it's a thermodynamic reactor; it's going to give you the thermodynamic product. Well, if we have a flow reactor, you can actually isolate transient intermediates that you can react and do chemistry that you could normally not do on a batch reactor, and that's exactly what we did with this tuberculosis drug that have the carcinogens in it. We generated the material quickly; we made a stable version of it; we generated the intermediate quickly, then consumed it without formulating the nitrosamines. So, those are some of the things I think about with regard to flow chemistry that we can actually benefit from as far as maybe looking at new approaches to making molecules that are going to give us new chemistry as well as new, more cost effective products.

0:41:05 It's funny, I had a great boss earlier in my career, and he said, "You know, Frank, once you made the product, nothing good can happen." [Rich laughs] And I think that there's a lot of truth to that, because the stuff goes into a batch reactor and it sits there heated for a long time, so if you can get it in and get it out, you not only reduce your capital footprint, but you also had a way of being able to improve the heat history of the product. So, that's one of the things.

You also mentioned about AI. One of the reasons why you reduce labor costs with these continuous processes is because you've automated everything, and the reason for that is—the good news about flow chemistry or continuous processing is you can make a lot of material very quickly. The bad news is you can make a lot of bad material very quickly. So, you have to be able to feed forward feedback control systems that are parametric in design so that you really understand the kinetics in the process of the method for making that material in a way that allows you to just run.

0:42:04 And then the other thing we do is we just developed some really innovative new ways of measuring product quality in real time, and that's another innovation that's taken place that we're working on for a process that we built for a drug called albuterol which is in short supply now. So, those are some of the innovations that you're looking at, not just in the continuous processing, but in the automation area and with regard to measuring product quality.

Then the third area you mentioned was AI. I think AI has a place here too. When we were working on this Pharmacy on Demand project with my MIT colleagues, we were using the literature database to identify all the different ways we could actually make a molecule, and then we're taking that information and then prioritizing them and figuring out which one was the best one based on specific criteria of yield, number of steps, carbon footprint, those types of things. And then we would take that information and we'd take what we thought was the best option, we would optimize it, then we would make the molecule.

0:43:04 Well, it was funny because the folks at NASA got real interested in it, because they're thinking, "Oh, if you've got this unit, you can actually use it for extended space travel to Mars." And I said, "Well, that's an interesting thought. The problem is if you don't know what you're going to make, how many starting materials do you need to carry on board with you, and how's that going to affect your payload?" My colleagues at MIT said, "You know, that Frank's a wet blanket."

Rich Bendis: [laughs] And they were looking for another grant at MIT, that's why.

Frank Gupton: Probably, probably. It was really interesting, Rich, and it got me thinking. And I said, "So, if you got this divergent way of saying, 'Okay I've got one molecule to make, and what are all the different starting materials that I could actually use to make that molecule?' What if we took that whole AI paradigm and flipped it on its head and say, 'Okay, what's the minimum number of molecules we need to make here in the United States to make the maximum number of starting materials for this process?'"

0:44:00 And we're actually doing that right now with AI. So, that's kind of a different twist on it, but it's all related back to our mission and the supply-chain issues that we're faced with. So, there are basically three buckets there. There's the traditional petrochemical feedstock, so you take that list of maybe there's 20 compounds that we come up with, you just figure out, okay, how many of those are in the petrochemical sector? And then you look at the ag industry and the renewable businesses that have other building blocks, and then lastly you look at fermentation technology. Anyway, that's the way we look at these things more holistically.

Rich Bendis: Well, thank you about the look into the future. It sounds like you have a heck of a lot more ideas that have the potential come to fruition. All it takes is money and resources, Frank. I think there's another company coming called Kinetic Processing. I don't know if it's a brand new one or a spinout from Phlow, but if you think it should have been named that, that means there's probably something there to create something around it, and who knows?

0:44:57

Frank Gupton: Yeah, I think it's gonna be an exciting time, and I don't think any one group has the answer. I think this is the interesting thing about where I am at this stage in my life, Rich: I know what I know and I know what I don't know, and I try to partner with people who know what I don't know to be able to allow us to achieve an objective.

Rich Bendis: Yeah, and the nice thing about being old like we are is that if you don't need to work, you're doing it because you want to be there. So, it's nice that you're still doing it, Frank, and being willing to contribute. I guess there's some things we might be able to talk about doing together, which

I didn't know all of this background until we actually did this podcast, so it's all about communication, as we started in the beginning. It's people talking to one another and communicating with one another, and then you actually learn about one another, right?

Frank Gupton: Absolutely, absolutely.

Rich Bendis: Is there anything that we didn't cover, if you have an open mic for a minute or two, that you'd like the listeners to know?

Frank Gupton: Yeah. Just in closing, Rich, I have a basic philosophy in my laboratory, and that is, "Make new mistakes." I'm thinking about the flip side of that, because we're not going to be able to solve the grand challenges of the 21st century when we're making 20th century mistakes.

0:46:05 I think this whole paradigm of—my wife will probably kill me for saying this—but this whole paradigm of retirement, I'm not really understanding what that's about, because our job, I feel like, is to transfer knowledge to this next generation so that they learn from our mistakes and they make new mistakes. And I think that's probably the single most important thing that I do here, is to make sure that they understand about all the stupid things I did in my career that they don't have to repeat, and they can make new mistakes. But I can tell you that the highlight of my day is coming into the lab and somebody runs up to me and says, "Look what I found." That's why I can just keep doing what I'm doing. Plus we've got great students here at VCU, the engineering school is pretty amazing, and I've just been very fortunate to, I guess, reinvent myself in this last stage of my life.

0:46:55

Rich Bendis: Well, I'm glad you're still doing it, Frank, and the other thing about being able to do what we do is that I feel that I'm able to be very honest with people when I interact with them now, because if I don't share the knowledge that I've gained over six decades or whatever the time is, then I'm doing them a disservice. Because the sooner you actually are open and honest with people today, the more they can pivot, self-direct, or whatever they need to do, because sometimes people won't speak honestly to them.

Frank Gupton: This is the other thing too, Rich. I didn't talk very much about my basketball background. I wasn't that good of a basketball player.

Rich Bendis: Where did you play?

Frank Gupton: University of Richmond.

Rich Bendis: Okay, the Spiders.

Frank Gupton: I was a Spider, not for long, but I had one of the best seats in the house. [Rich laughs] And of the things that I use every day is about building teams, and I think that's one of those skill sets that I had the good fortune of being associated with some really good teams and figuring out how to take different skill sets and put them together to be able to come up with a solution to some of these fundamental problems.

0:48:02

Rich Bendis: Yeah, I think when you talk about team building, the leader, like yourself, can only be as effective as far as your shadow is going to reach, and if your shadow won't reach out to other people then your leader is not going to be very effective.

Frank Gupton: Very good. I agree with you completely.

Rich Bendis: Hey, this has been really enjoyable, and it won't be the last time we talk, Frank. This has been a very interesting addition of *BioTalk*. We've been talking with Dr. Frank Gupton, as we have said, who is the co-founder of Phlow and CEO for Medicines for All, both making a significant contribution in the BioHealth Capital Region and nationally and globally, and we want to come back and check with you on a regular basis to get updates on all of the new innovative things you're working on, Frank.

Frank Gupton: Super. The only thing I would add to that, Rich, is don't forget VCU. We've got probably one of the most outstanding chemical engineering programs in the United States with some great faculty.

Rich Bendis: How can I forget it after just hearing all about it from you for about an hour?

Frank Gupton: There you go.

Rich Bendis: So, we won't forget about VCU, Frank. Thank you very much.

Frank Gupton: Thank you.

Narrator: Thanks for listening to *BioTalk* with Rich Bendis.

End of recording.