MEDICAL SUPPLY CHAINS AND NATIONAL SECURITY: MANUFACTURING THE FUTURE

Announcer 00:00
Please welcome the panel to the stage.

Chandresh Harjivan 00:28
Great. Thank you very much. I'm really excited about this topic today, talking about supply chains and manufacturing. I think what's even more exciting is that the panelists here, who we have, who I know extremely well, and so it's going to be really good interactive dialogue. We've got Eric, Nicolette, John. Two of them were my old bosses. John was at NIST when I was doing work for him. And then Nicolette was on National Academies of Science when I was working with her. Eric, I've just known for a very long time, who's a real problem solver in this space. So, it's going to be really good. Let me set the context. So, if you think about supply chains, people just expect their medications to be in the pharmacy, in the hospital when they need them. But too often that's not the case. It's for a number of reasons. We're seeing drug shortages increase this year. Over 200 drugs are currently in shortage. That's an increase over last year. And we're seeing the trend line going in the wrong direction, with more and more drug shortages. So, why is this? Right? Well, the reasons are pretty, pretty small, actually. The price of generics, which are essentially 90 percent of the medications that are prescribed in this country, we pay very little for. Now, that's a good thing in a way, because it increases access to medications. But then the economics of it forced a lot of players to consolidate or exit the market, and you get one or two players. If you have one or two players in the market and something happens, it could be a hurricane. When I was in the White House, we had a hurricane hit North Carolina, and we had a huge issue of getting sterile injectables because of that. It could be because of quality. We're hitting some quality issues with some products from China, and then—sorry, from India—and you're not getting cancer medications. We can also see geopolitical issues that come up. During the pandemic, India stopped exporting a lot of their drugs, and we didn't have access to them. So, a number of reasons are caused by having a very concentrated supply of medications. And because of that, when you need your cancer treatment, you may not be able to get it. There's a few ways of starting to resolve this, and this is where we get into the panel, but I always like to categorize this into a supply issue: How do you diversify that supply? How do you have guaranteed demand for it? And then how do we have innovation? If we look at the way generics are made, they're often made from very old processes, 50-year-old processes, 30-year-old processes. So, we need to spend a lot more time and money on innovation so that we can reduce the old way of making things and look at

new, cheaper, more efficient ways of making things. So, that's the intro. I'm going to get into the panel here, and maybe have each of them talk a little bit about their backgrounds. And I'll just tee it up. Where do you see the problem in supply chain? And more importantly, where have you contributed to solving that problem? And each of you have, right, or are. So, Eric, let me hand it over to you.

Eric Edwards 03:22

Thank you. Eric Edwards. I trained to be an emergency physician, but then got into the pharmaceutical industry out of college. And my—so I can talk louder.

Chandresh Harjivan 03:36

Oh. Oh. You okay?

Eric Edwards 03:39

Like I said, I trained in emergency medicine. *[Laughter]* So, for me, this problem has been a problem for a very long time. Currently provide medical direction for a volunteer rescue squad. Every single year, we've been dealing with a drug shortage. And I think it's really important for this audience to understand that when we're talking about generic medicines, not all generic medicines are created equally. So, for me, it is really important that we start talking about securing America's medicine cabinet from the perspective of what's essential versus nonessential. When you call 911, you expect that that ambulance is going to arrive and they're going to have access to critical, lifesaving medicines to treat your loved one. And unfortunately, today we are dealing with drug shortages for very basic, generic essential medicines. Most of them are sterile injectable products. And the hospitals are dealing with the same thing. It's impacting patients who rely on our workhorse chemotherapy agents. Just last month, for example, a plant in India faced a flood, and we now have several chemotherapy agents that are in shortage as a result of it, a single point of failure. And that's just unacceptable. So, for me, an essential medicine is any medicine that is necessary to sustain the health of the American population. And for us, we can talk about what that list looks like, but there are various lists out there. And for us, our focus has been on the active pharmaceutical ingredients and the starting materials to make them, for which many of these come from outside the United States, and India, even starting materials from China. So, that creates a national security risk. It doesn't matter if we're talking about our warfighters on the battlefield or we're talking about public health emergencies or future public health emergencies. We need to ensure that there is a set group of drugs that the American public can have access to and know that they're going to be reliable, the quality is going to be there, and that we don't have a single point of failure when that future pandemic or public health emergency arises. So, the company that I started, Phlow Corporation, has worked with the United States government to start bringing back manufacturing, but more importantly, focusing on these generic drugs, non-innovator medicines, where there has been very little incentive to innovate for many, many decades.

Chandresh Harjivan 06:14

Nicolette.

Nicolette Louissaint 06:15

Good afternoon. Nicolette Louissaint. I serve as the chief policy officer for the Healthcare Distribution Alliance. Prior to that, I ran Healthcare Ready as the executive director. Healthcare Ready being a public-private partnership on supply chain preparedness and response. Prior to that, served at the State Department, leading the portfolio in pharmaceutical trade and economic policy, as well as the Ebola response from the State Department, USAID lens. All that to say, most of my career in policy has been at the intersection of pharmaceutical trade and economic policy. So, understanding the supply chain has been central to what I have done. I am a trained clinical pharmacologist with a specialty in HIV

chemoprevention. I think, you know, one of the things that's really interesting is I think we talk about what may be broken before we talk about what works. And one of the reasons that finding solutions that are sustainable can be difficult is because there isn't sufficient appreciation of what is working in the system. So, I want to spend a little bit of time thinking about what is working. And I think as we carve this out, there are continuity-of-care aspects to this, which is the question of how do we make sure that the medicines that you need at the pharmacy every day are there? But there's also the national security lens, which is: Should there be an event that triggers additional need for new products, what we call medical countermeasures, or a change in trade flows, how do we ensure that we have plans in place and resources in place and possibly even sufficient inventory to be able to create a sufficient backstop? But I do think there's a lot that works. And I think the need to think about how things are working well is important to avoid policies and solutions that create unnecessary disruption in that part of the system that is stable. So, for the parts of the generic system that you all have touched on, I think it's also important to note that we have about 90 percent of the generics market that is stable and robust. What we also know is that we depend, in the affordability conversation, on a stable, healthy, robust generics market to be able to do the work of keeping the cost to the patient low. So, we're all incentivized to have a healthy and robust generics market. From the distributor perspective, distributors do the work of moving more than 10 million products a day to 400,000 sites of care.

Chandresh Harjivan 09:09

Just describe that for a second. Just how distributors work.

Nicolette Louissaint 09:12

Absolutely. So, distributors are the part of the supply chain that most of us never have to think about but always rely on every day. Distributors have done the work of moving, as I said, 10 million-plus products every day from their distribution centers, products that they are getting from about 1,500 manufacturers, and they are delivering those to the pharmacies, the clinics, the hospitals that depend on those products. And so, what that looks like on any given day is, if you're a pharmacy, you put in your order—8 p.m. that night—and when you come back in, there's a tote with the products that you ordered there the next morning. What distributors have been able to do is ensure that a pharmacy, for one, doesn't have to hold more inventory than they actually need. So, when we talk about a lean supply chain, part of the security and practicality of that is that hospitals, clinics, pharmacies are not holding on to months of product. They hold days of product. But it also means that pharmacies, hospitals, clinics are not doing the work of having to connect with 1,500 different manufacturers to get all of the products that they need. If you think about it from the lens of a pharmacist, if they then have to place 40 different orders to get the products that they need for the next day, how does that impact continuity of care?

Chandresh Harjivan 10:40

That's right.

Nicolette Louissaint 10:41

So, that is what we do. We streamline that process in a way that ensures that inventory is readily available for the downstream customer that that pharmacist that is going to have to dispense the product. But we also do the work of making sure that we are connecting with all of those manufacturers and maintaining those connection points.

Chandresh Harjivan 11:00

Right. And so, when there's a shortage or you predict one, how do you—tell us about some of the good stories there?

Nicolette Louissaint 11:05

If you've seen one shortage, you've seen one shortage.

Chandresh Harjivan 11:09

Yeah, that's a good one.

Nicolette Louissaint 11:10

So, if there—so I will use specific examples. So, if we are thinking about Hurricane Maria, I think Hurricane Maria is a really interesting example for a range of reasons. Hurricane Maria didn't just result in what we would refer to as spot shortages. Those are not shortages that—FDA-defined shortages where there is a lack of supply. Patients moved and then the meds that they needed weren't yet in the places where they had moved to. So, in Hurricane Maria, there was—and actually, one thing that's interesting about Maria is for those that remember the trauma of the 2017 hurricane season, there were three back-to-back hurricanes. So, we had Harvey, Irma, and Maria. And so when Irma was approaching, there were patients that were between the USVI and Puerto Rico that were moved to Florida. It was safer for them. There were dialysis patients, a large number of medically vulnerable patients. Well, what happens is two weeks later, you now have Maria coming, and they would be in the direct path of Maria. So those patients were then moved, after all of their kind of—the medical adjustments were made for them in Florida, they were then moved to Georgia. So, now you have a large contingent of medically fragile individuals, who have now been twice moved in the span of three weeks from their home. And we have to figure out how to make sure that the meds that they need are available to them in the places where they're staying. So that is an instance of a spot shortage. And I think this is where talking about the various drug shortages list, though very wonky, it's important. One drug shortage list, which you guys have referenced, showed that as a shortage because there was a need, the FDA drug shortages list did not show that as a shortage because there was available supply. What distributors then had to do in that scenario was work with the providers that were now seeing those patients, understand what the needs were going to be, and then route the product that they needed to those regions. All of that work happened in less than 24 hours.

Chandresh Harjivan 13:28

Yeah. That's amazing.

Nicolette Louissaint 13:30

So, that's—when you think about the spot shortages that happen in these various events. They take different forms, but that's essentially a picture of what it looks like. If you're thinking about a prolonged shortage, one of the things that distributors are going to do is to work with their customers. So, we've seen cisplatin and the platinum-based cancer drugs in shortage. Those are conversations that are happening. The goal is to make sure that equity is upheld in the system, which means those who need product are going to get the product that's available. And those that may normally order product, but may not have the immediate need for it are going to get less product. And what that means is that distributors are everyone's enemy for a couple of months until the shortage is solved. But that is the ultimate goal of what we are doing.

Chandresh Harjivan 14:24

That's perfect. John, tell us a little about the innovation side. Actually, John used to work at NIST, where I worked with him, and that's one of the most underrated agencies in, I think, the US government. They're so critical, and no one's heard of them. And so I would talk a little bit about the work you did there as well. But then the work you're doing now at ARPA-H as well.

John Schiel 14:42

Absolutely, yes. So, pleasure to be here and a pleasure to be on this esteemed panel to talk about this very important topic. So, I started my career at NIST, the National Institute of Standards and Technology. I was the first postdoc as we were kicking off a biomanufacturing program there. So, I was the lead on developing a reference material, which became the international standard for monoclonal antibody characterization. The NIST standards realm is extremely important in all elements of biomanufacturing. And I think we're seeing that grow more and more and more. Moving forward in my career, when the pandemic hit, we do have one relatively large extramural funding organization called the Office of Advanced Manufacturing. This is also at NIST. So, I took over a portfolio of pandemic response projects that was ultimately leveraged to NIIMBL, which is one of the Manufacturing USA institutes, and oversaw several technology developments there that were primarily geared toward the COVID-19 response. During that time, as part of OAM, I also worked quite a bit with OSTP, discussing some of the policies, and we wrote several bold goals documents, including one on supply chain. And so, I had an opportunity to really start to dip my toes into the policy landscape. But as we were writing those bold goals documents, I ran into the ARPA-H folks and I thought, you know, let's not just write about these bold goals, let's actually try to tackle some of them. So, I'm here today representing ARPA-H. I'm a program manager at ARPA-H. I might reference several programs from some of my colleagues. But for those of you that haven't heard of or worked with an ARPA, ARPA-H really tries to fund the over-the-horizon technologies. So, I always say high risk, high reward. But I try to visualize that or help people visualize kind of what that means. And I found one of the best things is, anybody played *Oregon Trail* when you were younger? Yeah. So, you've gotten past Chimney Rock, which is about where I grew up. You're at the Rockies, and you're about ready to go over the Rockies to get to the gold. And so, sort of the iterative next innovation that we need is over that first mountain range, right? And that's where, you know, NIIMBL focuses on what we need to really get to that next innovation to advance the field. And ARPA-H tries to go straight for the gold in California and basically jump over all of those mountains. We really try to fund these extremely high-risk, high-reward projects, knowing that some of us might get diphtheria along the way.

John Schiel 17:05

So, my particular interest area is really on horizon therapies. So, genetic medicines, like personalized cancer vaccines, N-of-1 gene editing, et cetera. And what I love that the panel has kind of brought to light here in the generics space is that when we're thinking about that space, we think about what has gone well, what has gone wrong, and how can we design manufacturing that we can first-shore this technology so that we don't ever have to worry about reshoring it in the future? And that's really where we're trying to design some of our genetic medicines programs. So, that GIVE program that I manage is really trying to develop the next generation of manufacturing for some of these horizon therapies. And it just so happens that I'm sure we'll talk about things like distributed manufacturing, AI-based process control, real-time testing. These are all the things that we're trying to build into this next generation of RNA manufacturing that equally cross boundaries with some of the things that we need in the generic space. So, there's a lot of synergy. And when we talk about these things, we think of splitting them into these commodity generic products and then these high-value, high-return products, like genetic medicines, but they have a lot of shared needs in the technical innovation space.

Chandresh Harjivan 18:17

Good. And I would say there's a QR code that you can ask questions. I can't see any of you because the lights are so bright. But if you submit questions, we'll read them out. So, we talk about national security. That's part of this topic as well. You know, I was on Operation Warp Speed. I sat next to the CEO, Moncef

Slaoui, the COO, General Perna, and we're hitting, during COVID, supply chain issues for the most esoteric things. Glass vials. I didn't know there was a shortage of sand in the world. There's actually a shortage of sand. We needed sand for the vials. From—we had to go to Singapore. We had to go to France for Cytiva bags. We had to go to Korea for bioreactors. It was really the world working together in unison to solve COVID. It's amazing to see the fragmentation of that right now, right? And there's more—every country is talking about onshoring. And there are so many dependencies in other countries, and they can often be used as leverage for politics, right? And for economics. And so, one of the worries is that if there are events, and we've seen this in critical minerals, we've seen this in other areas, that could be a leverage point. And so, they might not be explicit about it, but let's say there was going to be another conflict emerging. They could say, well, you're not going to get your precursors for some of these generic medications. And, you know, my whole shtick is that if you're not able to get your new iPhone because there's not a component, a chip, or whatever, you'll kind of complain. If your car is more expensive because of the steel tariffs, you'll complain. But if you can't get your insulin or your critical medic—you're going to die, right? So, it becomes a critical chokepoint in geopolitics. Maybe, Eric, back to you. You know, some of these drugs have been in shortage for so long. I think epinephrine is a great example. Can you talk a little bit about the work that you've done in solving how it started, why there is an issue, and what you were doing to address epinephrine?

Eric Edwards 20:09

Yeah, sure. And first and foremost, I do want to mention I love the first-shoring concept because today's innovators are tomorrow's generics, right? Eventually, things go off patent, and I think everyone needs to recognize they're not mutually exclusive. So, solving for the future now is going to be helpful for a resilient supply chain later. So, when I got involved in this, we were focusing on a set group of medicines for children's hospitals. Pediatric medicines are disproportionately in shortage. They're also—the economics there are less favorable than adult medicines because of volume. So, sometimes you're not getting the right medicine at the right concentration. You have compounding pharmacies in children's hospitals that are having to compound these medicines to get them into certain infant formulations. And we were set up to start making some of these critical medicines differently to serve children's hospitals. Then COVID hit, and we looked at the list of medicines, and we were amazed at the overlap that was going to be needed to support COVID-19 patients. And we're talking about basic essential medicines like norepinephrine, epinephrine, or epinephrine to support blood pressure; beta blockers; neuromuscular blockade agents, the drugs that you use to intubate a patient; and other benzodiazepines for sedation. All of these medicines were made abroad. And even though we might have a supply of finished dosage forms—what I mean by that is the vial or the tablet or the syringe—from five different manufacturers, they might be receiving the same active ingredient from one manufacturer. So, a single point of failure really does disrupt the entire supply chain across multiple finished drug manufacturing providers. And we started to map that. In fact, we partnered early on with the United States Pharmacopeia, USP, to build a supply chain map, and we started noticing that there's a list of drugs that are disproportionately at risk. One of those drugs was epinephrine. This was a drug that was near and dear to me: my first company, my twin brother and I invented a competitor to the EpiPen called AUVI-Q. And we built and sold that company. And we got our supply from Boehringer Ingelheim out of Germany. But then they changed their supply, and the majority of the epinephrine in this world was coming from Taiwan. And so, we looked at this drug and said, how can we make this better through advanced technology? And what we found—and this is the case with many small-molecule generic drugs—is that no one had actually looked into the chemistry for decades. There was no reason to do so. For a generic manufacturer, it's follow the old recipe, get it on the market, repeat, rinse, et cetera, over and over again. And for us, it was what new technologies are out there to help us

improve the chemistry? And how do we look at the pharmacoeconomics so that we might actually be able to compete on price versus an Asian country that—where there are low labor costs?

Eric Edwards 23:10

And so with epinephrine, we were able to come up with a new process, and then we partnered with a finished drug provider, and we brought this drug back to the United States' soil for the first time in 40 years. So, there is a model here, but it requires partnership with the United States government. It requires us to think differently about different manufacturing technologies. And you really have to have the time and the capital that's willing to work on an industry that is not incentivized to improve their manufacturing industrial base. The generic manufacturers throughout the world aren't incentivized to act—they aren't incentivized to improve their quality; they aren't incentivized to use new technology. It truly is a race to the bottom and pricing that has—that has failed the American public. So, how can we look at that differently? Look at unique public-private partnerships where we can start to reshore one drug at a time and protect the most vulnerable components: those starting materials, intermediates, or active pharmaceutical ingredients. And so that's what we did with epinephrine. Now, the company, along with several other companies in partnership with the government, are tackling these drugs so that we don't face what we faced during COVID-19 through that next public health emergency.

Chandresh Harjivan 24:23

So, there's a few questions coming in. One relevant to you is asking about cheap labor in China or the cheap cost of manufacturing in China, and India, I would say. Can you talk about the human capital costs here as well? Either skill sets or just labor costs? And how much does it cost to make something here versus in India or China or Taiwan or other places?

Eric Edwards 24:43

Yeah, it's more than twice the cost to make something here. For sure. And I think that one of the things that we don't think about: we look at economics for generic drugs on a unit cost basis. What we don't look at are the cost to the system when there's a drug shortage. There are hospitals throughout our country now who have to hire an employee, a director of drug shortage management. And when you have to switch a patient from one chemotherapy to another chemotherapy, those switching costs have real implications on the health-care system. So, for us, it's about looking at what is the unit cost comparatively in the United States versus an Asian country? What can we do on the chemistry to improve those costs? What can we do on automation for the manufacturing floor to reduce the labor output required? And then finally, how do we change the way we look at the health-care system and distribution and supply so that we can streamline to the patient some of these medicines and be more competitive overall in the future? But, certainly from my perspective, 75 percent of the problem is on the cost side of things. When a vial of a life-saving drug costs less than a bottle of water at an airport, we have a problem. And what often happens is we even have our federal government, we have the VA, we have the DoD, CMS reimbursement mechanisms that do not reward where the drug is coming from, or the quality and reliability of that drug. They reward the lowest possible cost, period. And that is something we have to fix as a country. I'm encouraged that the EU actually just introduced the Critical Medicines Act. Next year, they will now be incentivizing manufacturers, taking into account both quality and location of manufacture for their own national security and supply chain resiliency efforts. And I think investment is going to follow that. Investment will reward quality and reliability and resiliency. I'm hopeful that with this new Congress coming in, that we can turn some of these things that have been, candidly, executive actions, and single points of do this or else into actual bipartisan action to secure our supply chain.

Chandresh Harjivan 27:03

Yeah. I mean, this is where the problem starts, right? Because, if you look at contracts to purchase medications, basically the purchaser can break the contract any time to get a cheaper generic. And so the manufacturers don't have any continuity in demand. They could get cut off any time. And that's where you see a lot of players exiting the market. Or, where you've got state intervention, like we see China or India, the state really come in and subsidize these to own the market. And that creates concentration, and that creates a political leverage point, as well. So, I think we have to get beyond buying the cheapest drugs. And these are—these drugs are so cheap, if we increased even—and we've talked to the manufacturers—increased by even 10 percent, it would be nominal to the health-care system, but we would secure that supply. They just need a small incentive to make those purchases, but we're still struggling with that, as well. When I was at the White House, we did start something called Bio-5, which is working with Japan, Korea, the EU, India, and the US to both diversify supply and aggregate demand, and focus on innovation as well. And the idea is that we'd have each country kind of focus on one type of class of drugs. So, Japan would work on beta-lactams. We've had Europe focusing on penicillins, et cetera. But then there'd be kind of an aggregated demand as well, so the manufacturers would have predictive markets for that. The rest of the world is kind of moving in that direction, leaving the US out because we haven't seen a lot of action.

Eric Edwards 28:24

I think it's a good point on the United States doesn't have to make everything.

Chandresh Harjivan 28:29

It can't.

Eric Edwards 28:29

It's impossible for it to make everything. We need to choose the drugs that make sense to make here: complex active ingredients, certain controlled substances. There are certain essential medicines where we need to have that pharmaceutical sovereignty ourselves. But we also need to rely on allied nations. And we need to be sensitive to the national security risk and play out the scenarios of if, God forbid, there were a war or another trade dispute and we couldn't get access to components, what are the medicines that are going to matter most to you all, to your families, to our hospitals, when we need them?

Chandresh Harjivan 29:01

Yeah.

Nicolette Louissaint 29:01

Can I just jump in for a second?

Chandresh Harjivan 29:03

Of course. Please.

Nicolette Louissaint 29:03

So, I think there are a couple of things that are important here. As far as diversification of supply, I think it is really important to think about not reshoring to the United States as a strategy, but being able to think about how our diversification strategy includes the United States.

Chandresh Harjivan 29:25

Making something in North Carolina… *[Inaudible]*. Yeah, that's right.

Nicolette Louissaint 29:27

Let's be very intentional about carving that out and explaining the differences. Overconcentration in the United States is as much a problem as overconcentration in Asia. But I also want to think about how we frame the existing market. When we see shortages in the United States, what we also know is that the shortages picture in the EU is far worse. And part of that is because the reimbursement picture is very different. And so, as we are thinking about what is happening on the purchasing side, we have to be very clear-eyed about the fact that we are talking about products that are reimbursed as a bundled payment. And so, if we are not willing to invest more, and that includes how we are reimbursing for these drugs, it is then unreasonable to ask hospitals and pharmacies and clinics, the same facilities I was just talking about, to be able to pay more, even if it's a 10 percent increase. Because again, that is at the expense of their margins. We are hearing hospitals talk about what they have experienced since COVID and not having a full recovery. So, again, when we're thinking about what it looks like to see federal investment, that has to include the reimbursement picture. And that may also be a factor in how we're thinking about certain products, at least these GSIs, the generic sterile injectables, and others, how they are being reimbursed as a bundled payment versus as individual products.

Chandresh Harjivan 30:57

So, talk a little bit about that—

Nicolette Louissaint 30:58

Certainly.

Chandresh Harjivan 30:58

—because one of the questions was, "Who sets and negotiates the prices for drugs?" Can you talk a little bit about that? It's a complex question.

Nicolette Louissaint 31:06

Well, yeah. Because I'm like, which price? So, I guess let me go back to you, which price? I think that part is important to how I answer it.

Chandresh Harjivan 31:16

So, I would say—so, let's look at a generic medication, right?

Nicolette Louissaint 31:20

Sure.

Chandresh Harjivan 31:20

Let's look at an ACE inhibitor, right, that's coming in? Who's the one who's purchasing it? The hospital, the GPO? Who negotiates the price with the manufacturer? And then, why is it so low?

Nicolette Louissaint 31:33

Okay. So, I just wanted—so, the price a patient pays, I think is sometimes where we're trying to end. But I think there's a difference when we're talking about the price, which price we're talking about. I will give your example, but I think we should start with the pharmacy example, because there is a difference between what happens on the hospital side versus the pharmacy. In the pharmacy picture, we have purchasers, including distributors that are working with those manufacturers. They are looking at a range

of factors. So, we often talk about price, and Hatch-Waxman, the law that governs this and has created a generics market, centers this on price. But there are—

Chandresh Harjivan 32:14

Which was a good thing in many ways.

Nicolette Louissaint 32:15

Yeah. No, it's a great thing for affordability. I think what we're realizing is there's an "and" there that says price and other things are factored in. Distributors factor many of those things in. So, these are in many cases long-term relationships. So, quality, resilience, business solvency, these are things that are looked at among others. And there's an agreement on price. Yeah. So, that is the first price that is set going downstream to the pharmacy. The pharmacy gets to determine the price that they want to pay. If they don't like the price of manufacturer one, they are, again, when we're talking about placing those orders, they're making decisions about the products that they want in their pharmacy. So, that is, kind of in a simple way, how the prices flow on the pharmacy side. On the hospital side, it is more complicated, because you have group purchasing organizations that are able to use their buying power. Which is a good thing to be able to negotiate, so there's kind of a guaranteed volume. And with that guaranteed volume, they're able to negotiate. As I understand it, they're looking at similar dimensions of understanding kind of who they want to partner with as manufacturers for the products that would be the formulary of a hospital.

Chandresh Harjivan 33:38

Okay. That's very good. So, John, why is health care so expensive in the US? *[Laughter]* No, that wasn't the question.

Eric Edwards 33:46

Yes, John.

Chandresh Harjivan 33:48

That was not the question. So, the question here was, "How can the private sector bring innovation concepts to ARPA-H? And what does successful partnerships and program execution look like?" And I would add, ARPA-H is what, two, three years old? I mean, it's pretty amazing to create a new agency, right? And so yeah.

John Schiel 34:02

So, we're about four years old, now.

Chandresh Harjivan 34:05

Four years old.

John Schiel 34:06

The office that I'm in, Scalable Solutions, is a little over two. Kind of a tradition of mine, I guess, is being the first in an agency. So, I was also the first program manager in Scalable Solutions. So, we literally spent six months getting set up, and now we're really launching several programs. So, kind of the mechanism—there are two mechanisms. So, anyone can bring an idea to ARPA-H. So, if you or your company has an innovative idea that is shooting for the gold in California, we have what's called an open ISO, Innovative Solutions Opening, which I don't like as a name because I'm from NIST, so I think of International Standards Organization. But this is a way for folks to quickly bring us an idea. It's a six-page proposal, so very small. That'll go to a PM. We'll review it, and then we'll invite a full proposal if it's an idea that's within

our mission space. The majority of our funding goes out in program calls. So, this is an idea that a program manager like myself brings into the agency. We pitch that to the agency, mature it over a couple of months, and then we'll put out a larger call for ideas. So, we will set the metrics, the milestones that we think we need to get to solve a particular problem in the ecosystem. But we really look to the innovators outside to bring the solutions to us. So, we'll say, in a year, we think we need to be here; at two years, we think we need to be here. But we really do then rely on industry to propose the ideas of how they're actually going to make those things happen. So, I'll bring up one program that was recently launched by a colleague of mine, James Coburn, that's in this space. So, he came up with a program called FASTPASS. And so, one of the critical challenges with generics, and really any drug product, is sterility and quality of that product as it comes into the United States or gets into a pharmaceutical stockpile, et cetera. So, his idea was, wouldn't it be great if there was a way that we could actually test that quality in the vial as it sits on the shelf in real time? So, yes, we have a pharmaceutical manufacturer's lot release that says we tested the quality as we're shipping it over. But what if we could just open up that vial, not destroy it, put it into a series of analytical technologies and say, "Yes, this is still sterile; it still has the quality we anticipated," essentially fingerprinting that drug? So, he recently put out a call for proposals, again with very, very well-defined metrics, to look to the community to say, "Give us your crazy ideas. What technologies do you have that we can bring together to look at a vial of drug and say, yes, it is still what we think it is, without putting it through the typical lot release that we would do for a drug product?" So, that's the type of kind of crazy, innovative program ideas.

Eric Edwards 36:43

In essence, you'd prevent the recall before it occurs.

John Schiel 36:45

Absolutely.

Eric Edwards 36:46

Interesting.

John Schiel 36:46

And provides visibility in theory early for a drug shortage that may be coming. Because we might find, okay, this batch of drug is no longer meeting the quality specs that we need. In theory, you could see then tracing that to other API suppliers and saying, okay, maybe there is a broader contamination issue. And this could actually even help to forecast drug shortages before they happen as well.

Chandresh Harjivan 37:10

Good. We have a very prolific set of questions here. This audience is very—one question back to you now, which I think is in your wheelhouse, is, you know, biosimilars, right? And the question is, why have—the exact question is: "Biosimilars offer a way to bring advanced therapies to more patients, yet the pricing is often not much below the innovator molecule. Why is that?"

John Schiel 37:30

Oh, this is also a toughie. So, I was actually on the first biosimilars panel that the FDA had as an external advisory committee, and I remember one of my colleagues on the panel stood up and said, "I'm voting for this biosimilar, but if we don't see the cost-cutting that we plan to have in the future with this biosimilars market, I'm going to be very disappointed." Very interesting thing to say at an FDA advisory panel. But, point well taken. So, I think part of that is, as we're making these biosimilars, one, I'm an analytical chemist, so we have a huge analytical dossier that we need to do to actually show biosimilarity to a product. If we

get to interchangeability, which means the pharmacist can actually interchange one dose or the other, you get even more detailed in the analytical package that you need, and that actually is a huge cost on biosimilars. But the other part of it is we're still typically using the same technology. So, monoclonals are typically made with CHO cells. The manufacturing process is essentially the same.

Chandresh Harjivan 38:35
We're still using CHO cells? Chinese hamsters? It's not allowed anymore? Is that banned?

John Schiel 38:38
No, no, no.

Chandresh Harjivan 38:39
That's a bad joke.

John Schiel 38:39
It's still good. It's still good.

Chandresh Harjivan 38:41
Yeah.

John Schiel 38:42
So, I think we need to tackle this from several angles, right? So, certainly the manufacturing technology, you don't have to use the same cell type to make a biosimilar. You can actually make a biosimilar using a totally different manufacturing platform as long as you show the analytical biosimilarity. So, we do need to think about potentially changing the manufacturing paradigm in that space to help lower costs as well.

Chandresh Harjivan 39:06
That's great. Another question for you, Eric, is looking at upstream. So, the question is, "We've been talking about finished dosage forms over here quite a bit, but how much of our exposure is further upstream in APIs or key starting materials, and who are we dependent on?" Why don't you characterize all that?

Eric Edwards 39:24
So, unfortunately, the vast majority of the starting materials that we rely on, that go in, feed the intermediates, and then feed the active pharmaceutical ingredients, are from nations that may not have our interests or best interests at heart, including China. And a lot of the active pharmaceutical ingredients and the intermediates that are made in India also rely on China for those starting materials. One of the challenges that we face as a country is—if you open up your medicine cabinet or a pharmacist opens up a Pyxis unit, and anyone pulls a vial or any kind of finished dosage form off and looks at the manufacturer, that country of origin, as it relates to the active ingredient but then all the way upstream, is so opaque. You actually really don't know where things come from. And so, I think there's been a lot of effort to try to map the supply chain to understand where our true vulnerabilities lie. This panel is about national security, in part. So, for us, we should be thinking about: What are those points of failure that could occur? God forbid we were in a war, where—just using the rare disease example—excuse me, the rare earths example, and chips example, and battery capacity, and some of these other national security industrial bases—essential medicines and the starting materials needed to make them should be in that same category. How do we figure out which ones we need to make in allied nations? And how do we figure out where single points of failure exist, where we need to incentivize other manufacturing technologies? There's a lot that's happening that I'm very, very pleased to see, that pairs biomanufacturing to help support starting material manufacturing that can lead to small molecules being manufactured in the United States. An example of

that: We had a partnership between Phlow and a company called Antheia that figured out a biomanufacturing process for thebaine, which is a precursor to a lot of the opioids that we rely on, and its antidote, naloxone, you all know from the brand name Narcan. If we can think about how to use technology differently, map the supply chain, understand where these points of failure are, I think we can get ahead of some of these national security interests. And then I think there's a huge promise for innovation in the future. And I love the technologies of whether it's coming in from an importation perspective at a shipyard, or we see things before it even gets to that active ingredient, because we saw this plant have a fire in Asia, and we know what the implications are downstream—a lot of this could be solved for. But we are just starting that process. There is so much we don't know.

Chandresh Harjivan 42:17

It is amazing when you buy a T-shirt, right? It'll say where it was made, the carbon footprint, whether it was forced labor on there. It's very transparent. When you put a pill in your mouth, you have no idea where it came from. It's ridiculous.

Eric Edwards 42:30

And I think, you know, we should be thinking—like, I don't know about you all, but we're getting all these catalogs now in for Christmas, right? And there's, like, all these different…

Chandresh Harjivan 42:39

You get physical catalogs coming in?

Eric Edwards 42:40

Like physical catalogs. I'm still getting, and for shopping. And there's certain things that when you're shopping, you are not going to sacrifice on for quality. Sometimes you want to buy your furniture from Dollar Tree. And other times you're like, that's not, probably not a good idea, depending on where you're putting that furniture. We're talking about patients' lives here. And we need to be sure of the supply chain, of the quality that's coming in. And we need to make sure that we don't face a shortage like what is happening right now, where every single cancer institute in this country is reporting chemotherapy drug shortages right now. In part because, last month, Pfizer's Hospira and Zydus partnership resulted in a flooded plant that's going to be knocked out 'til late 2028, at the earliest. So, that can't happen when we're talking about patients' lives. And that's what we're talking about, having that visibility and transparency, and getting on top of this for the future.

Chandresh Harjivan 43:42

Yeah. It's also interesting about, you said quality. I mean, you trust that your medications are of good quality, but there's been many instances where the drugs—FDA is really good at approving drugs; it's not always so good in ensuring the quality of drugs. They don't have the resources to go to India to look at the facilities. And even if they do, the Indians know they're coming and they do a cleanup of the facility. It's very predictive, right? And so I think we need to get better at doing spot monitoring of drugs. The FDA needs to get more resources to do better inspections, as well. But, Nicolette, you know, when you look at drug shortages, how do you address them? So, I think I would break it up into three different areas. I know—you know, I'm a pharmacist myself, and often we would have a shortage, and we would simply substitute one drug for another drug. Patients wouldn't even know it in the hospital, but you just substitute it, right? How do you look at that in terms of when there's drug shortage and managing a drug shortage?

Nicolette Louissaint 44:34

So, from the distributor perspective, oftentimes the surveillance and the ongoing conversation with manufacturers is a part of the strategy. And while pharmacies, hospitals, others are holding a few days of product, distributors are holding far more than that. So, if there is the ability to forecast a shortage or a potential shortage, there are a range of different tools that distributors can choose to use. One of the things that is important is—and I think the national security lens is different. And so right now what we're talking about is kind of steady state: What happens? It is really predictable what happens when the general public—and I'm thinking general public, downstream customers—know that there's a potential shortage. Everyone that has the ability to buy product tries to buy it all up.

Chandresh Harjivan 45:35

Yeah. Yeah. That's right. I remember, my wife's a pharmacist, and we were—I'm like, "Is there a shortage of this?" And she's like, "No, we bought a whole bunch of it." I'm like, "You're the problem."

Nicolette Louissaint 45:43

Right. Right. Right.

Chandresh Harjivan 45:43

Because she was stockpiling. She sent me a photo.

Nicolette Louissaint 45:45

Exactly. It's called hoarding. And people do it with bacon. They do it with cereal. They do it with toilet paper. But they also do it with meds. It's a human behavior. And so, one of the things that distributors will do in order to avoid that is to limit orders. That is a very unpopular approach. Imagine, it's like when you go to Costco and they tell you that you can only buy five super packs of 24 rolls of toilet paper, right? Like, there are two people in your house. Do you actually need more than that? But it's the exact same thing, right? And so, that is one of the things that distributors do. The other thing that distributors will do is work with other manufacturers. A big part of where we spend time is having those conversations. And so, if there are other manufacturers that are available, there are conversations: "Hey, what does it look like for you to plus up? Are you able to turn this line back on?" One of the things that we should not do is pretend that part of finding solutions is not a part of everyone's day job, right? So, if a manufacturer knows that they can go from running an 18- or, in some instances, a 12-hour cycle, and they're going to shift to 24 hours, and they're going to change their processing so that they are running continuously, those are the types of things that do happen, right? And so, allocation is not going to be lifted, right? But those are things that are happening to put in additional supply. Another thing that distributors are going to do, they're going to be in conversation with the FDA, just like manufacturers, right? And so, part of that is, what can the FDA do? Is the FDA in a position to temporarily allow for importation of other products from other countries to alleviate that risk? Is the FDA aware of other manufacturers that do have approved ANDAs that are able to then go online? Like, those are the conversations that continue to happen. And so—

Eric Edwards 47:48

I think it is important: steady state versus non-steady state, right?

Nicolette Louissaint 47:53

Absolutely.

Eric Edwards 47:53

During COVID, you mentioned it earlier, India shut down the exportation of 26 active ingredients.

Nicolette Louissaint 47:59

But Eric, they also did that and then realized that they were shutting down for active ingredient and they needed finished dose product from us.

Eric Edwards 48:07

That's right, they did. And the good news is we got part of it resolved, but they also withheld over 3 million albuterol inhalers on the tarmac for a period of like two weeks.

Chandresh Harjivan 48:17

And COVID vaccine.

Eric Edwards 48:18

And COVID vaccine. So, I do think it did resolve itself, and I think it's important to have leverage on both sides.

Nicolette Louissaint 48:24

That's my point.

Eric Edwards 48:25

Which is a huge point. But there might be others where they don't care, right? Or that the system's not going to work the way that we want. I do think that when a natural disaster takes out a plant, you don't have much leverage.

Nicolette Louissaint 48:39

Well, so, two different things—

Chandresh Harjivan 48:42

It's getting good now. This is good.

Nicolette Louissaint 48:42

When we're talking about—get the popcorn—when we're talking about a natural disaster taking out a plant, like what we saw in North Carolina, that's exactly the reason that we caution against geographical concentration, even in the United States. The reality is that even in the United States, if we see a single plant go down, we are going to see disruptions in supply, right? So, I think that's part number one. Part number two is when we are talking about geographical diversification and allied nations, we should be very intentional about—and this is my State Department hat coming back on—about delineating where our allies are. India is a tremendous ally on the pharmaceutical trade side, right? Like, that is the reality. I also think it's important for us to make distinctions. We're talking about China. We're talking about India. We're talking about the EU. There are differences in the diplomatic relationships that we have and what those allied relationships look like on the pharmaceutical side. So, again, I just—it's not as popular, but nuance here is important. From a national security side, though, I think we need to be thinking about a range of different events. There are notice events. There are no-notice events. There's geopolitical conflict. There's even disease outbreaks, and I think part of what we're touching on is when there are disease outbreaks that cause countries to close their borders, that is a different strategy for the United States, because what we find out is that even allies can be irrational.

Eric Edwards 50:17

Yeah.

Nicolette Louissaint 50:18

And that's what we saw with India, right? And so that I think is a different type of planning. And one thing that we haven't touched on yet is how stockpiling plays a role here. But that is a big part of the strategy. A lot of the solutions that we're talking about are being phased in over time. And I think in a decade, I hope, we'll be in a different place than we are right now. But as we're getting to that place with the strategic investments that we can see from the federal government, the private sector and others, it is important to think about the strategies that we can use today to hold more finished product and even API on hand.

Chandresh Harjivan 50:54

So, that, actually—yeah, and I think the geopolitics are changing, right? So, I actually don't care if my drugs come from China or I was in Canada behind enemy lines.

Nicolette Louissaint 51:03

I care that they work.

Chandresh Harjivan 51:04

Just yesterday, you know, we don't know who our enemies are. But you don't want to rely just on one source, whether it be North Carolina, Ireland, or China. You need diversification of the supply chain. One of the questions here was about drug expiration and whether we're leaving drugs that would expire and wasting those. I think maybe a, you know, adjacent question for the team. And you, Eric, start with you, is around looking at the stockpiling of API and KSMs now, as well. Do you want to talk a little bit about how that works?

Eric Edwards 51:34

Yeah, so we embarked on a project with the United States government to create the nation's first strategic active pharmaceutical ingredient reserve. It's called the SAPIR. And I think you raise a ton of excellent points around: until we have domestic capacity or until we've eliminated the single points of failure, what can we have as bridging strategies? One is we can secure enough a critical active ingredients and starting materials on US soil that have shelf lives that far exceed sterile injectable finished dosage forms. Some of those last, you know, some of the finished products last a year. You can have active ingredients that last up to 10 years. And you can recrystallize the active pharmaceutical ingredients. So, we are playing a role among many other players in trying to shore up this new idea of, let's get the most critical components here as a bridging strategy until we get these other things worked out, in case of a more significant geopolitical event.

Nicolette Louissaint 52:26

And from a national security perspective, we're always going to need stockpiles, because the reality is, if there is a no-notice event, there's going to be a surge in demand, whether it be localized to a particular geography or across the entire nation. That's going to require an uptick in product. And that's something that we know and understand.

Eric Edwards 52:46

Including toilet paper.

Nicolette Louissaint 52:47

Including toilet paper, and bacon, I would add. So, I think that is a strategy that we will always have to invest in is making sure that we have sufficient stockpiles.

Chandresh Harjivan 52:58

Yeah. And also I think, working in the White House, in the Situation Room a lot, and one of the big worries was around cyber facilities as well. And they could be made anywhere, right? And you could create disinformation. You could simply stop a manufacturing facility with different issues to just cause confusion. And we're seeing some of that happening already in other critical infrastructures, but medications is like the heart of the beast, right? Because the impact that it has as well.

Nicolette Louissaint 53:21

But I think the other thing about the health-care industry as it relates to critical infrastructure risk from a cyber perspective, that 400,000 sites of care point that I raised, means that health care is more fragmented than other critical infrastructure industries.

Chandresh Harjivan 53:36

That's a strength, in a way.

Nicolette Louissaint 53:37

It's a strength and a weakness because it means that cyber targets are more abundant. And so if you look at what we've seen, even in public school sectors across the nation, we started to see public school sectors get hit because they're small and they could. So, think about what that means for rural America, for example, places where it is fragmented. And that is a strength because that means that there's one clinic within 25 or 50 miles. But that also means if that one clinic goes down because of a cyber event, what happens to those patients that rely on that facility?

Chandresh Harjivan 54:13

All right, so we've got five minutes left. A question here is: "What solution would you want to see moving forward at the federal level in the next year or two?" So, what recommendation—start with you, John, and be quick—but what would you like to see happening from a policy level that could help mitigate supply chain issues?

John Schiel 54:30

Yeah, I mean, I definitely think that as I hear this conversation, there's a lot of elements to this challenge, right? So—and there's a lot of solutions too, right? There's stockpiling, there's stockpiling APIs, there's regional or even global geographic diversification, and so we kind of have to get to our next level of homeostasis, right? And it's probably going to be a mixture of all of those things. And somebody's going to come up with a great idea of how to provide that visibility. So, how can we have privacy-preserving architecture to really better understand a broader swath of the supply chain for critical medicines? Maybe that's a solution. When I think about diversification, I think of technologies that, you know, right now, if we say we're manufacturing API X and we're using—everyone's using this manufacturing technology, maybe we diversify that.

Chandresh Harjivan 55:20

Diversify technology rather than the products.

John Schiel 55:22

Absolutely, yes. So, like the manufacturing process. So, we have one project that we're funding where we're actually using wheat as one of the main raw materials. So, people who have done manufacturing with wheat germ extract for years at very tiny scales. And we had someone come to us with a great idea that said, "Hey, we can actually scale this technology and make small-molecule APIs because we found this key unlock to actually make that possible." This is the WHEAT program. So, from a policy side, I really

think continued investment and innovation is what I hope to see really help this field move forward, because there are a lot of challenges and we're going to have to start to mix and match those in some way, shape or form, to really have a holistic solution to this challenge.

Chandresh Harjivan 56:07
Okay.

Nicolette Louissaint 56:07
I don't just have one, but I'll give you part of my list.

Chandresh Harjivan 56:11
I think there's a break after this, so we have lots of time.

Nicolette Louissaint 56:12

I feel like I need a scroll. I need to be able to, like, unscroll. Like, "Here are my ideas." I think we need to look at CMS reimbursement in a real way. Part of that is we do need to look at how some of these products are reimbursed. We also need to look at how we are funding and incentivizing facilities to hold on to more product, as well as thinking about how we are encouraging them to work with manufacturers to think about incentivizing resilience and supply. We need to think about expanding FDA authorities. That's a very real part of this conversation. We need to think about what it looks like for the FDA to make decisions about what they do with the information they have, how they can use the data that is available to them to do the mapping and visualization work that they need. Do we need to also expand FDA funding to be able to take the data that they have in finished doses, go all the way down to API, and make decisions that they need to make around API, as well as the ANDAs that are being unlaunched? I also think FDA needs funding as it relates to inspectors. So, it's great to say, "Resource so that the FDA can do more inspections." It's better to say, "Let's continue to fund the FDA inspectors that are overseas as well." Commerce plays a role here, and I don't think we've had the opportunity to talk about that more. I think ASPR needs an expanded SNS. Under the late Paul Mango, who was at—right—who was at HHS during COVID, talked about this idea of SNS 2.0, thinking about SNS being prepared for catastrophes and also having a role in some of these lower-level national security incidents, but knowing that they need the resources to be able to do that. I think we need to pick that back up and think about what it looks like to fund it. A lot of these strategies around resilient supply need a guaranteed purchaser. That guaranteed purchaser needs to be the VA. It needs to be the DoD. So, that is a part of my list. I'm happy to go on, but—

Chandresh Harjivan 58:03
I like that.

Eric Edwards 58:04

Well, she hit the majority of mine. I will add one: with Hatch-Waxman, what created the generic supply chain was six months of exclusivity for the first to file. And I wonder, with this list of 86—or not every drug, but an intentional list where we see a national security angle—what would it look like to provide an additional level of exclusivity? If—and this is for the future, this is talking about those innovators that turn into generics—if a manufacturer committed to keeping that drug on US soil, and it was made end-to-end here, and if it connected to a national security angle, where we need this to be available for our warfighters or for a future public health emergency, if you gave them an additional level of exclusivity, six

additional months of exclusivity on the marketplace once they file for that first generic, what would that do to bringing back manufacturing in the United States of America?

Chandresh Harjivan 58:56

That's great. You know, I would just close this out to say that I think we do have much better visibility into the supply chain. We need more visibility. I think tariffs actually have done a lot to force companies to know where their products come from. I'm not a big fan of tariffs, but I think we're—just because of tariffs, every country now is getting better at knowing where their products are coming from, including drugs. Knowing where the problem is doesn't create the solution. So, we do need more guaranteed purchases. We need more investments in those bottlenecks and diversifying those bottlenecks as well, so that we don't have that patient who has cancer not able to get that critical medication. Thank you to the audience. Sorry I wasn't able to answer all the questions; there were so many of them. Please reach out to any one of us with your questions offline, in person, at the next break that we'll be having in a few minutes.

Eric Edwards 59:43

Thank you.

Nicolette Louissaint 59:44

Great job. Thank you.

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