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WEBINAR

REBUILDING THE U.S. MEDICAL SUPPLY CHAIN

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P R O C E E D I N G S

MR. WEST: Good afternoon. I'm Darrell West, Vice President of Governance Studies at the Brookings Institution. And I would like to welcome you to our forum on Rebuilding the U.S. Medical Supply Chain. So, COVID has posed dramatic challenges for the world. There have been over 3.7 million deaths, globally, and disruptions of virtually every aspect of daily life. This has created enormous issues, in terms of public health and emotional wellbeing, yet it also has highlighted a number of problems, in terms of the drug and the medical supply chains and manufacturing capacity.

Last year, there were major shortages of medicines and personal protective equipment. Many hospitals were overwhelmed with sick patients, and at the same time doctors and nurses did not have the medical equipment and protective equipment that they needed, in order to safeguard themselves. Today, we plan to discuss pharmaceutical drug manufacturing and supply chain logistics, in light of the COVID Pandemic. We will examine the obstacles to manufacturing drugs, and producing medical supplies in the United States, and possible solutions to those barriers. We, obviously, need to make progress on COVID, and also put the United States on a much better course, in order to weather any future health crises.

To help us understand these issues, we're delighted to have five distinguished experts, with us today. Tony Sardella is an adjunct professor and senior research advisor at the Olin School of Business Center for Analytics and Business Insights, at the Washington University in St. Louis. He is a co-author with Paolo De Bona, of a new paper on ways to incentivize domestic drug production to combat medicine shortages.

Rosemary Gibson is a senior advisor at the Hastings Center, and the author of a book, entitled "China Rx." Spiro Gavaris is President of Specialty Generics. David Thompson is a co-founder and chief technology officer of Continuity Pharma, and also a professor of Chemistry at Perdue University. And, finally, Edward Price, is a consultant and former president and CEO, of PCI Synthetics.

If you have questions for our panelists, you can email them to us, at events@brookings.edu, or you can Tweet at #USSupplyChain. So that's email, events@brookings.edu, or Tweet us at #USSupplyChain, and I do want to note, we are doing this event in partnership with the Olin School of Business at Washington University, and we appreciate its support of this forum.

So, I want to start with a question for Tony. So, you co-authored a new paper, at Washington University, on domestic drug production. What did you find in your research, and what recommendations do you have for moving forward?

MR. SARDELLA: That you, Darrell. First, it's a pleasure to be with you and everyone, today, to discuss this incredibly important topic. Our purpose, myself and Dr. De Bona, who had performed the research, our purpose in doing, in goal, was to do a comprehensive literature review of both the industry and the complexities of the industry, to gather many of the different points of view and suggestions and recommendations, that have been made, to understand those and assess some of them, in regards to their potential to create solutions for more resiliency in our supply chains.

I can tell you, in doing the review, it's a very complex industry, as many of us know. Obviously, it's unique in regards to it's high regulation to ensure the safety of our supplies. But there was certain areas that we concluded, around recommendations and suggestions for further analysis, that could help to relieve the strain on the supply chain and act in regards to solutions. The first we found, very much so, was this -- we were regarding the topic of reshoring and domesticating the manufacturing of our supply chain, the clarity around what does it mean to be made in America?

This is not unique. This is a very similar topic of discussion many years ago, decades ago, around the automotive industry. But with certain cases, it's become quite unclear, as to the definition of made in America, when it comes to pharmaceuticals and APIs. So, clarifying that was one of our major findings.

The second thing was the need for incentives and financial support to the industry. The economics of many of the essential medicines that we were at risk of being short, and in some cases were short, the incentives in the economics just do not allow for significant manufacturing in the United States. And so, one of the key elements is the ability to incentivize current potential manufacturers who have capacity or capabilities in the United States.

Secondly, financial support, in a variety of different means, and this is not just for existing manufacturers, but even through -- to support, financially, the breakthrough advanced manufacturing techniques, and of course we have Dr. Thompson, who can speak to that, with his incredible research in that area, but even incentivizing and financially supporting the ability to bring these advanced

technologies to bear, as we consider manufacturing in the U.S.

Another part we found that may be somewhat simple, but yet quite striking, was defining the market. A lot of the challenges, economically, in manufacturing, in the United States, is lack of clarity of what is the market around the essential medicines that should be produced or desired to be produced, in the United States. I'm very pleased to see, just a few days ago, with the White House announcement of a working taskforce, to identify what those might potentially be, and to derive a list, and recommend them.

And then, in addition, we found ourselves very constrained for a very different reason, during COVID, and that is the ability -- the same safeguards that make the supply chain so rigorous, thorough, well managed, and also protect the safety of our public. They also become impediments when you're trying to be very agile to stand up production, in the face of a pandemic. And so, as such, the ability to streamline, potentially the regulatory process, both during those states, but also for some of the new manufacturing technology, would allow for significant areas of solutioning for building more resilience.

So, those are the core areas. We view them very much as suggestions and recommendations for further review. They're very complex, each of them, but these were areas in our research, we found, were absolutely areas that needed to be look at, to build greater resilience.

MR. WEST: Great summary, Tony. Thank you very much for that, and, those of you who are interested in reading the longer paper, you can go to the Washington University website, the Olin School of Business, and there's both the longer paper, as well as a short summary of it, as well, and I'm sure people will find it very informative.

So, Rosemary, you pointed out that the problem is not just the supply chain, but how we get materials for drug manufacturing. So, what are the problems that you see in this area?

MS. GIBSON: Thanks, Darrell, very much, for the chance to be with you today, and, Tony, thank you for your paper to jump start this conversation. It's great to see colleagues on this panel.

I'll just make three points, Darrell, and that is I think we have to realize how centralized the global supply chain is, for the components to make thousands of medicines that people rely on in this country, that make our hospitals run. When the Coronavirus was just heading this way, last February, I

was with a group of manufacturers around a dinner table and asked them. So, here are some basic COVID drugs that we need, you know, that the depressor agents, the -- like the epinephrine and others, and antibiotics, like azithromycin.

I said, so tell me, the core components to make them, where are they sourced? You run around the table with these manufacturers, with a 150 years' experience, and each of them said, 90 percent of the global supply is sourced in a single country, mainly China. So, in the middle of a pandemic, you have, you know, hundreds of -- 100 countries competing, for the same products. And so, what's so important is to recognize that degree of centralization.

And, Tony, to your point about made in America. Unless we have some diversification throughout that supply chain, from the raw materials to chemicals, all the way up to finished drugs, you know, we won't have that degree of self-sufficiency, which I think we need for the basic essentials. We don't have to make everything here, but what's really important that we have to have, in -- during a pandemic, or we saw what happened when a freighter blocks the Suez Cannel, for a week. You know, these are products that are essential for life, so, they're different from other commodities. So, that's one point about centralization.

And I think it's also important to underscore how we got here, that this is not a -- and, Tony, I think you alluded to this. This is not a normal marketplace, with transparency and competition, transparency on price, and transparency on quality. And by the way, there is a lot of serious problems with quality.

Now, I'll just say the focus of today that I'll be talking about is on the generic drugs. And I think most people don't realize that generics are 90 percent of the medicines that run our hospitals, the ones, when you go to the drug store, that's what you'll get, and these are the commodity products. So, that's a very important thing to talk about. So, there isn't a level playing field, when it comes to competition. We have states -- countries with industrial policies, like China, that subsidize their industries to billions. So, if all of us here, and those watching, wanted to start a manufacturing company here, in the U.S., we're not competing with other companies in other countries. We're often competing with companies that are hugely subsidized by their governments.

And, finally, I want say so, from a policy point of view, we have some choices to make, as

a society, for our public health and also for our security. And that is, do we think we should have the ability to make at least some antibiotics, here in this country? Do we need and should we have, as a country, to make pain medication? There is a panelist here, Spiro, he'll be talking about this. In Europe, there was a shortage of paracetamol, which is basically generic acetaminophen, during a pandemic. You couldn't get it. Again, because that product, a lot of the core components are sourced in a single country, in Asia.

So, the question is, do we think that these products are so important? You know, in economics, there's a thing called public goods, and I would submit that things like antibiotics, that is a public good, to stop the spread of infectious disease. That's why we invest in vaccines. What is remarkable, that the United States has virtually no capacity to make antibiotics, what you give to your kids for ear infections.

We can't make them here because we don't have the manufacturing facilities anymore. So, I think, that's a really fundamental question for policymakers. Should we have some basic amount of manufacturing capability, fully end to end. To me, made in the U.S. means we've got to be able to make these essential products, ones that are essential for life, from the very beginning, those starting materials, to the very end, because, when a pandemic hits, we're on our own, and I think that is one of the lessons. So, I'll stop there, Darrell, and I really look forward to a great dialogue with everybody.

MR. WEST: Thank you. That's a great point about centralization and the problems that flow from that. So, Spiro, I'd like to come to you. So, Rosemary has pointed out that the materials for many drugs come from China. We know a lot of the drug manufacturing capability is in India and China. What steps should the United States take, in order to boost its domestic drug capability, and what are the drug supply challenges that you see?

MR. GAVARIS: Sure, and I just want to say thank you, Darrell, for having me today, and Tony for the wonderful paper that you wrote, to shed light on this topic, and the needs around it, some recommendations. I think, just to ground the group, you know, I'm the President of Malecross Specialty Generics Division. I'm over top of the largest U.S. API manufacturer -- manufacturing site, as well as the only Western Supply of Acetaminophen.

And so, we are one of the top four suppliers of acetaminophen, globally, and we're fully

vertical on our acetaminophen, such that we, you know, we've been able to, you know, keep the U.S. out of the same troubles, that we saw in Europe, during the pandemic. When you look at what we're facing, right now, I think a lot of the issues have been framed well, right? Over 90 percent of the raw materials are coming from overseas, very centralized. It's not a level playing field, from a cost basis, from an environmental regulation basis.

And this is in the generic segment that's being the hardest hit because it's the most heavily commoditized, and we're looking at, you know, pennies per hundred count is the difference between a product being made in the U.S. and a product being made Ex-U.S., right? We can make these things very inexpensively here, but with all the focus on drug pricing, even within the generic market, if you're a couple cents more expensive because products are being subsidized, lower labor cost, lower environmental regs, then, you know, Ex-U.S. products are being sourced today, and that's the challenge.

I think, you know, there's been a lot of focus on things, like expanding capacity in the U.S. and looking at new technologies, and those are all valid areas that we need to look at. What I think is underappreciated is the spare capacity that we have, you know? You know, there is a lack of diversified manufacturing in the raw materials. Of the 103 manufacturers of API, globally, that have 30 or more drug master files, you know, kind of a way to differentiate big manufacturers from small, only four are in the U.S.

But many of the -- you know, but most of those companies are being underutilized, right now, in terms of capacity. As volumes have moved overseas, the plants we have, you know, are at spare capacity. And so, you know, one of the first things we need to do is look at, how do we define the market, and create sustainable markets, create the right incentives, for manufacturers, for -- of API of finished dose, and potentially, you know, the distribution channels, so that their incentive to distribute and pull through U.S. made products, inclusive of U.S. API Manufactured products.

You know, I think, that's going to be one of the most critical things because you want to do that, before the capacity we have is decommissioned. We're seeing consolidation in the markets, right now, with the API manufacturing, and we need to act quickly, so that -- before we lose more capacity that's readily available. Right now, our -- we estimate our spare capacity on our site, if it were a standalone site, would be the fifth largest U.S. API manufacturing site in the country, and so, there's

plenty of capacity we need direction on, as to what are the essential medicines that we're going to identify, and are there ways, in which that we compete on a more level playing field, and create those sustainable markets, as we move forward.

I think other things other things that we need to look at and acknowledge is that, you know, we don't need to make everything here, as Rosemary said, and we don't need to make full market demands here, right? We don't need to be fully self-reliant. We just need to have a critical mass, so that we can be resilient, during times of need. It's easy, from a manufacturing perspective, or feasible I should say, to ramp up, from covering 20 or 30 percent of the U.S. market to covering a full market, versus zero, right?

And this is where we were at, on the majority of products, where we did a analysis, where over 80 percent of the product that we utilize here, as generic medicines, essential medicines, there's not even a single U.S. supplier of the raw material. So, you know, we don't even have a domestic option, for the bulk of these, and so, finding a path forward, where we can increase the capabilities in the U.S., and we can broaden that, is essential, and then acknowledging that we're not going to be fully self-reliant, you know, strengthening our partnerships with our Ex-U.S. partners, you know, to fortify those during times of pandemic, I think, is also something that's critical, so that you build your capabilities and your ability to withstand, you know, stresses, like we saw during the pandemic, both domestically and through better partnerships overseas.

MR. WEST: So, it sounds like there are a lot of worrisome issues here, that we need to be focusing on. So, David, I know you've talked about the need for better infrastructure, in regard to manufacturing. What are the challenges that you see?

MR. THOMPSON: Well, first off, I'd like to point out that Continuity Pharma, the company that I've founded and launched out of efforts in my academic lab, is focused on providing and ensuring availability of essential medicines, and particularly medicines that are not only essential, but that we can actually speak to the quality issues, that either -- that all of our previous panelists spoke about.

What I'd like to -- a couple of points that I'd like to get across. Number one is that so-called continuous manufacturing of active pharmaceutical ingredients is a reality. There are seven approved -- FDA approved agents, that were produced by continuous manufacturing, one of those being -

- including product of the API, itself, continuously. There are dozens of known methods for making some of these essential medicines, in a continuous manufacturing manner, through publications or work that is being presented at meetings. This is both in the generic drug space or making those generic APIs, as well as what much of the pharmaceutical industry is focused on, right now, is getting continuous processes into their new chemical entities, so new drugs.

They're not looking backward to bring this technique to generics, but more for producing new materials. And there, I guess, following that point, and something that's really relevant to the time, it may not be widely known, that technology, the first continuous lipid nanoparticle, an siRNA Product, patisserin, was approved in 2018. That core technology is what enabled the manufacturer of the COVID-19 viruses. So, in other words, if you've had the jab, you've benefitted from continuous manufacturers. So, this -- it's a technology that's already scalable, and within our grasp. It just hasn't -- that's the vaccine applications, siRNA applications, are more biopharma. Really, the challenge here is what do we do about these legacy products, the -- that we still rely on?

So, I think, an important point, that is not fully appreciated, is that pharmaceutical manufacturer is very inefficient. It's a 150-year-old industry. The methodology largely has not changed. Techniques have not changed much, and so, it is 1,000 times less efficient than things, like producing bulk chemicals or petrochemicals. There's -- and that's measured on kilograms of waste generated, per kilogram of product, so, incredibly inefficient when you think of it in that context, and so, really, kind begging for new technologies to impact this problem.

The one other aspect that makes it difficult with continuous manufacturing being more generally accepted, in small molecule synthesis, is the so-called, you hear it a lot in conferences, in this area, is the need to "make the business case". So, it's that same focus on diving to the bottom of the cost curve that is really kind of choking, you know, killing in the crib, the ability to bring these new methods to bear, in the production space. And whether that's just, you know, dollars and cents, or resistance to change, whatever you want to call it, I think my key point here is that it -- we have the capability, it's just figuring out how to deploy it in -- to serve the patient population, in the U.S.

I am fully on board, with the point that was made earlier, about needing to level the playing field. In my view, perhaps a bit pollyannaish, but I would think that, you know, it doesn't take a lot

to imagine something, like an underwriter's laboratory, a third party, that is spot-checking materials, and actually assessing their quality, and coming up with a quality scorecard, that now becomes a tab two, that goes on every bottle that is produced, so that, now, the consumer is the one who is empowered with the knowledge, that this is a manufacturer that hasn't gone out of spec, a lot of times, and caused shortages. And really, it's kind of this Lewis Brandeis thought of, you know, sunlight being the best disinfectant.

The more information you have, that you shed on the product, and doing things, like collecting real information, rather than just trusting that the product is inspected, it's on the shelf, I think, would, from my perspective, would be a significant step in the right direction. You know, I think, there -- it will likely come out in the Q & A, but I think it's going to require both public and private investments, and whether that's in terms of, you know, creating consortia or perhaps strengthening process patent protections, so that you can -- so that those who create better, more efficient processes, can better defend their processes. So, there are a lot of different facets that I think are worth considering. So, I'll, I guess, leave it at that.

MR. WEST: It sounds like we definitely need a lot more innovation in this 150-year-old industry. So, Ed, you've discussed pricing issues with pharmaceuticals, and the low share of the money that actually goes to manufacturing medications. So, what are the problems that you see here, and how can we address them?

MR. PRICE: Well, I was the Founder and President of a mid-size generic API manufacturing company, and I definitely echo Spiro's sentiments about capacity. We, too, had excess capacity, in fact, for the better part of ten years, we were developing new generics, on an annual basis, and pretty much all that came to an end in 2017, when, simply, our customers couldn't afford to develop any new products for the U.S. market, and then we simply began manufacturing the products that we had approved.

And what was ironic about that whole situation was the fact that, over that same period of time, we saw that on, literally, on a monthly basis, our customers products, which were generic drugs, decreased in value in the marketplace, successfully, year -- year after year. And, ultimately, if you look at, you know, the way that we distribute drugs here, in the U.S., it's quite apparent as to what the situation is. Both the finished dosage and the API manufacturers get about 15 cents, for every dollar that's spent, in

the United States.

The pharmaceutical industry, in the U.S., is about a \$500 billion industry, but 85 percent of the prescriptions are generics, and that 85 percent of the business represents only about a \$100 billion, and of those \$100 billion, the manufacturers only get about 15 billion. So, there's a huge disconnect, and, of course, the bulk of the money is actually going to wholesalers, distributors, pharmacy benefit managers, and the pharmacies, themselves. And, certainly, what's unique is that we're the only country in the world, that actually distributes drugs in this way, that we have all these different layers between the manufacturer and the patient that opens up their medicine cabinet to take their medicine every morning.

So, I'm convinced now, more than ever, that if we really want to have a paradigm shift in this situation and really move the needle to improve the situation, we have to start talking about beyond tax incentives and other ways to make manufacturing more attractive in the U.S. We really got to start to unlock that incredible value, that's sitting there, which could be, in fact, shared between manufacturers and patients, if we actually have the will to change how we distribute drugs here, in the U.S.

I also want to make another point, and that's regulation, in general. As a mid-size pharmaceutical manufacturer, of course, we're regulated by the FDA. We also -- we're regulated by the DEA and other controlled substances that we made for medical purposes, you know, but at the same time, we're also regulated by the EPA, and the Department of Labor, and the state -- all the plethora of state agencies, as well. And I can tell you, we're also -- that, over the last 10 to 15 years, the regulatory environment, just in running a manufacturing business, is completely different and has grown.

Common sense regulations is what needs to be brought back, and I'll give you a really quick example. There was a time where many states, here in the U.S., were working toward toxic use reductions of materials, in their facilities. But, of course, you have to file a Drug Master File with the FDA, on your manufacturing process. So, if the environmental authorities, want you to change your process, okay, and they're going to fine you if you don't. And if you do, you're going to get in big trouble with the FDA, for changing your process.

So, these -- that's just a quick example of the disconnects that are -- that exist between all the different Federal and State Agencies, that regulate this business, and, quite frankly, make it very difficult, you know, to do manufacturing here. And, of course, in many respects and parts of the world,

India and China, specifically, you know, you have tremendous government support, and you don't see those disconnects in place. So, just a couple of additional comments.

MR. WEST: Perfect. Sounds like there are lots of complications in this area. So, now I'd like to move from problems to possible solutions. So, I -- and I'm going to ask this of each of you. If you were advising Congress and the Biden Administration, what would you tell them about what the U.S. needs to do, in order to improve this situation? What are the highest priorities? What are the most important initiatives? And perhaps, Tony, we can start with you.

MR. SARDELLA: I think, capitalizing on the comments of both David and Spiro, regarding that there is capacity in the United States and there is novel technology, I think one of the areas, from a long-term resilience and sustainability, is to invest in the development of these technologies and the expansion of existing capacity that is in the United States, but may not be pointed, obviously, because of economic reasons, to the particular molecules, the essential medicines that are important for overall public health and resilience of our population and citizens.

And so, I would say that, while there's been some attempts to emphasize the distribution and allocation of investment funds to the development of current capacity and advanced manufacturing technologies to satisfy the gap and the need that we have. Interestingly, Darrell, in our preliminary, these are still preliminary, we've been doing additional research on the profile, the research quite indicates that there's strong possibilities that these advanced manufacturing techniques can, in fact, make it economically viable to produce this product in the United States. That's first.

The second thing is the data suggesting that it's far more bleak, I think Spiro and Ed point it out, as well as Rosemary, far more bleak, not just the essential medicines, but you might consider important medicines for citizen and public health, where we have no U.S. suppliers, no U.S. suppliers. And so, while they may not be in the crossfires, right now, within the pandemic, to point investment in those areas, as well, to build that capacity in the United States.

MR. WEST: Thank you. Rosemary, your thoughts on what you would like to see the United States do.

MS. GIBSON: Thanks, Darrell. I think, while this is a very complex area, I think there are solutions, and it doesn't have to be that complicated. I've been following, very closely, as I'm sure some

of you have, what a group of large hospital systems have done to set up a nonprofit, called Civica Rx, and they're -- the hospitals have decided that we're going to use our procurement dollars, that we would spend on essential drugs, we're going to use them in a different way and buy differently. We're going to buy a quality product, and we're going to be assured of a supply that's not interrupted.

And so, they all put in, and -- at this nonprofit not capital, but the counterpart for capital in a nonprofit. And they went out and they found trustworthy manufacturers. They paid them a fair price. What we have now is a race to the bottom price, and that's not sustainable. That drives people out of the market. Pay them a fair price, fully transparent, they actually inspect the facilities, and they have the product tested, something which does not happen now, with so many generics.

And in the first year, they, through contract manufacturing, with trustworthy manufacturers, they were able to deliver 20 essential generics to their member hospitals, 1,400 member hospitals, started by the Mayo Clinic and others. Kaiser Permanente is a part of it, with their 10 million members. In the next year, another 20, and the following year, another 20. And they hope, within five years, to supply their member hospitals with 100 essential generics that have been -- I'll call it messed up.

The supply chain is really messed up. I think people really need to understand that. And when I've given grand rounds at hospitals, I say, why do you tolerate these very large companies, the ones Ed alluded to, this is, you know, speaking the truth here, how do you tolerate suppliers that supply you with drugs that are poor quality, sometimes harmful to patients because they're not made properly, and in perpetual shortage? Why do you do that? And so, it's like anything else, if you want to fix the market, just buy differently.

So, my recommendations have been, in testimony to Congress, and the House, and the Senate, is that, well, let's use our procurement dollars, that -- our taxpayer dollars. Why are we spending money to buy blood pressure medicines from the military that has rocket fuel chemicals in it, which is exactly what happened. In 2018, it was discovered it was going on for about, at least, four years. Let's use our procurement dollars that the VA, and the Strategic National Stockpile, and the military need. And even, you know, the buyers, you know, Medicare is the biggest payor, not directly, for basic generic drugs, and that was something that was pursued, but it was pulled back on, recently, which I think is really unfortunate.

Just like anything else, if you're the customer, demand a better product, not what we're getting now. The quality problems are -- and I'm an optimistic person, but I'm seeing -- they're getting worse and worse. I shared with this group the other day, when we were doing our practice run, a very wonderful physician, very -- at a very prominent institution, his wife got a blood pressure medicine, and her blood pressure spiked to 190, which is like -- that's death zone. He went back to the pharmacy and the doctor, and got a different generic, and her blood pressure was normalized within hours, and that was a product coming from China. Nobody's testing this stuff, and yet these are all the ones that are nonvalue added between the patient, the manufacturer, and then everybody else. And I think it's going to happen anyway with -- look at Amazon Pharmacy. Do you think they're going to tolerate all those middlemen taking all their money? No, absolutely not. So, we need innovation in the distribution system to save money. It's great to have -- I totally support continuous manufacturing, but we have to get that product to market, to the people who need it, and going around this very nontransparent system that doesn't add value. And Civica is a way of doing that.

So, you really have to care about the products that you're using, that you're supplying to patients. You know, this is life and death stuff we're talking about here. So, this is fixable, if we just use our procurement dollars differently. And it makes it -- that's what's challenging to talk about. The problem can be solved, but the solutions, a lot of people don't agree with because it takes away some part of their pie. But I think we really have to be honest about this. We really want to ensure our public health security and to build trust.

You know, a lot of people are losing trust in their medicines. This kind of stuff that we're talking about, with poor quality drugs and how these big middlemen -- they are actually buying generic drugs that have received -- their companies have received FDA warning letters. That's a big deal, if you get a warning letter, Spiro knows that, Ed knows that, and, sometimes, repeated warning letters. That's like Costco saying, we're going to, you know, buy tires from a manufacturer that's gotten letters from the Federal government, saying, you know, you've got problems, and these tires could blow out on the highway, going 65. This is what we're doing with our medicines.

So, it's fixable, if we choose to use our procurement dollars differently. And as David mentioned, it doesn't have to break the bank, especially if we can put the real value in the manufacturing

side, and that way we rebuild trust. It'd be great public policy, and it's absolutely doable, but we need the political will to do it.

MR. WEST: Great ideas. All that makes a lot of sense. Spiro, your recommendations on how we can do a better job here.

MR. GAVARIS: I think the first two panelists are going down the right track. When you look at it, it's about sustainability of the markets. It's about getting the right incentives and funding into the right hands. And when you look at the cost of -- the cost differential between buying at a fair price and the race to the bottom, it's very minute, right?

When you look at the percentage of what we spend in generics, you know, Ed quoted it at 15 billion, I mean, you could use basic math, and say, if you took a certain percentage of that generic spend, across the country, and funneled that into what are the essential medicines, it'd be a fraction of that 15 billion. And when you think about what we need to do to be sustainable, 20-30 percent of the market would create a very large critical mass of manufacturing, and that's in line with what Medicare and Medicaid percentage spending is, usually between 20 and 40 percent, for a given product, depending on the age population.

So, when you look at this, it's within the realm, if policyholders want to do it. You're talking less than a billion dollars, in terms of incremental subsidies to, you know, stabilize the entire healthcare system, across a broad spectrum of products, and, you know, you'd create tens of thousands of jobs within the U.S., at the same time, bringing U.S. manufacturing jobs back, you know, and that would be tremendous. And so, we've just got to think smarter about how we're using our dollars, as a government, about where our interests lie, about not just how inexpensively are we dealing -- are we procuring products. But what's the purpose of defense?

When you look at what we spend to defend the country, on a military basis, you know, it's tremendous. When you look at what this incremental spend would be, on a healthcare basis, it is a extremely small percentage of what the government spends, to date, through its programs. And then, so, for that small incremental, you'd have tremendous benefit, in terms of reshoring capabilities, stabilization of markets, and improvements that speak to many of the things that our panelists are saying today, and so, it's possible.

It takes work because it's changing the systems that are in place today.

That's going to come with friction and opposition, you know, and so, it's working through those challenges to understand what's in the best interest of our, you know, of our citizens, and the people here, and patients across the country, and how we can do that. And so, it's not going to cost much, dollarwise, it's about changing the machine, so that we can put the right levers in place, as Tony mentioned earlier, defining what is made in America, defining what are the key products, you know, setting up the parameters for how do the incentives flow. Does it go through reimbursement channels? Does it go directly to manufacturers? But just creating the right mechanisms that efficiently, you know, incentivize companies, and as those incentives are in place, we'll find ways to leverage new technologies, we'll find ways to leverage the existing capacity, we'll find ways to expand the capacity, if we know there's a market to address, that we can do so at a fair price, and with, you know, competing against competitors who are working under the same parameters that we are. And that's what we do today, right now. I mean, the largest suppliers today, in the U.S., of APIs, you know, are largely controlled substance suppliers, where the borders have been controlled. Policy has been in place to protect those entities. They're competing amongst themselves. The prices are highly genericized, very low. Medicines in that space are very affordable. If you look at other policies you can put in place, you'd have a highly competitive market, in the U.S., with very affordable meds, a very small incremental, and it speaks right to what Ed had mentioned earlier, as well as the other panelists.

MR. WEST: It sounds like those are all investments that really pay off for people. David, what is your advice, either to Congress or President Biden?

MR. THOMPSON: Well, actually, it -- the prior speakers have really brought up some excellent points. So, I will speak more to the continuous manufacturing aspect of this because I think the idea of leveling the playing field and using different, essentially, market strategies to incentivize the manufacturer, domestically, both make a lot of sense to me. I think what may not be appreciated is that continuous manufacturing technology has embedded in it a sensing and control system, a feedback loop, that allows for the, essentially, assurance, in real-time, that the product you're manufacturing is in spec. And if it's not, because you have real-time information, you divert to waste any material that's not in spec.

So, that gives you a data package that -- of assurance that can track the product, that I actually alluded to earlier, gives an opportunity for remote check-in on health of a process. If you're a

regulatory agency, I still think having some kind of end of the line product assessment, spot-checking, is essential to assure quality. Rosemary mentioned that that's what Civica is doing for its patient population. I think that's very much a step in the right direction.

But from a technology standpoint, the idea of having continuous systems are actually, often, much more compact, than current batch methods. And what that enables is a number of things, of not only a smaller footprint at existing manufacturing sites, but the possibility of actually regionalizing some of the production, which achieves a couple of things. It gives you redundancy in the system, just like the internet. When OneNote goes down, you have the ability to still push signal through different channels. And it also provides some agility, in terms of different agents that you might be -- that might be in need, that are simply harder to achieve, when you're operating in a batch mode, on scale.

And as Rosemary pointed out, your tanker boat gets stuck in the canal, right, because you're operating on such a large scale, you need those starting materials on a large scale, and they have to be scheduled months in advance, which is what, actually, we're still experiencing in our supply chain, are the ripple effects of COVID impacting us, and we're still feeling shortages that are coming about, from those antiquated methods.

So, I guess I'll come back to one other idea I put out there, of this quality scorecard idea. I think that's really important for informing consumers. But I think the final prescription that I would make is actually the kinds of investments in people because running continuous operations is going to require a new workforce, or at least workforce that's been retrained or -- and certainly up and -- the up-and-coming generation needs to be learning modern methods of production, rather than some of the more antiquated methods. So, it's people, that's high school through post-grad, investments in equipment, and control systems, and software that's going to make these processes run as efficiently as possible.

And that efficiency, I want to come back to that metric earlier, kilograms of waste divided by kilograms of product, that's where the pharma industry is right now, in terms of 1,000, 1,000 of waste for every kilo of drug. That has environmental impacts, and the more we can actually get efficient methods in place, those so-called e-factors can be reduced into double digits. There are processes that have -- for API that have been driven down into the 18 or 12 e-factor, so, orders of magnitude, less waste, which is going to have less environmental impact, require less energy to drive those processes.

And I guess that the one other point, I guess, is to find some way to incentivize, from a founder of a company that's focused on bringing new manufacturing techniques, finding a way to either cooperate or have whatever IP it generates be more protectable and not lifted by competition are the kinds of things that I think need to be thought through, and I'd welcome any new ideas on how to achieve such a thing.

MR. WEST: Thank you. And I do have to say, I like that Suez Canal boat example because it's an apt metaphor for the global supply chain, of how a problem in one area can create havoc in a lot of other places, and, you know, we seem to be having the same situation, and we -- in regard to drug manufacturing. Ed, we'll come to you, get your recommendations, and then we'll take some questions from the audience.

MR. PRICE: I've actually been saying, for a number of years, that leadership is needed here, at the highest level. So, what I would like to see happen is I would like to see the FDA basically come up a list of the top 50 essential medicines that should be produced in the United States, okay? And companies like Spiro and mine began paying user fees to the FDA, in 2013, to the tune of north of \$400 million a year, and it's increasing every year. So, the resources are there for them to do this.

This taskforce would identify these drugs, and, at the same time, identify the technologies like David, and the excess capacity at facilities like mine and Spiro's, that could actually manufacture them, and then using Rosemary's idea of pulling together the marketplace of the Federal government, the VA, partnering with organizations, like Civica, and actually create a marketplace because, you see, when you develop a new API or a new drug product, it's three to five years of investment, from the inception, or conception, I should say, all the way to approval.

So, understand that if you have a marketplace, where the cost of the products are increasing monthly, every month, year over year, and it takes you three to five years to bring a product to market, who's going to make that kind of investment? And that's why we stopped developing generic drugs in 2017. So, if that combined spend could go to U.S.-based manufacturers, and say, look at -- if you take the risk and develop the product, we're going to give you a contract and pay you X amount. Okay. There's not a manufacturer in the United States that wouldn't take that deal because there's so much uncertainty in the marketplace right now, that if there were -- if you put certainty into it, you'd be

happy to do that. And so, I think that, you know, overall, you know, that would be, really, be the best way, you know, leadership with the FDA.

And I think -- and lastly, actually, well, I should mention, as part of this idea of mine to work, the FDA would have to give priority review to those manufacturers in the, you know, the United States. That is something they never do. And, of course, regulatory agencies, around the world, give priority review and status to their own domestic companies. The FDA is the only one in the world that, quite frankly, doesn't. They're very agnostic when it comes to national. But if you, again, if you really want to make some changes here and you want to improve things, okay, if we can create the marketplace, if we can create the financial incentives, and we can create the regulatory environment to support manufacturing that are made in the U.S., as Spiro said, the incremental costs to actually do this is, really, incredibly small.

MR. WEST: Okay, great. It's a great synthesis of a number of different ideas. So, now, we're going to move to some questions from the audience, and I would ask our panelists to keep your answers brief, just so we can get to as many questions as possible. So, Douglas has a question. He says, the term rebuild presupposes that the U.S. once had an effective and efficient supply chain for pharmaceutical drugs and PPE. He wants to know when was that the case, and then why did U.S. drug manufacturing decline? Anyone who would like to address that?

MR. PRICE: Well, I can just comment from an API standpoint. You had major pharmaceutical manufacturers, like Pfizer, and Merck, and all the well-known names, they had tremendous facilities here, in the United States. Then, there's plants, okay? And basically starting in the late '90s and throughout the last decade, you had these contract manufacturing industry, which began growing significantly, around the world, and most of the major U.S.-based pharmaceutical manufacturing decided to outsource the manufacturing, from high cost to the U.S. to overseas manufacturers, where they could transfer their technologies and manufacture them cheaper.

MS. GIBSON: Okay, can I just jump in on that, Darrell?

MR. WEST: Sure, go ahead.

MS. GIBSON: Yeah, back in the 2000s, there was an article in the *New York Times* about the last penicillin plant closing in the United States, so, but it didn't say why. So, in "China Rx," I did

a real deep dive on that. And it was a Bristol Myers Squibb plant, up in Syracuse, that used to produce 70 percent of the world's supply. Well, thanks to industry folks from Europe, they had data showing where, you know, there was illegal trade practices.

China dumped penicillin raw material on the global market, right in 2004, I have the slides showing it, and they kept the price low, for four or five years, and that drove out the last U.S. plant, the Bristol Myers Squibb plant. It drove out the India -- the last Indian -- India can't make antibiotics because they don't have the capacity anymore. So, then, the price went up.

And the other thing that was interesting is, you know, who thought that trade and the tariff policy would have an impact on our drug manufacturing? And I documented that when we opened up free trade with China, within four years, that's when the last penicillin plant closed, the last aspirin plant. We can't make aspirin anymore, acetylsalicylic acid, we can't make vitamin C anymore, ascorbic acid, and thousands of other things.

So, our trade policy has a profound impact, and, frankly, we have to enforce, too, our antitrust laws because the vitamin C case was another case of cartels. So, that was another factor of these unfair trade practices that contribute to us losing our manufacturing base. In the U.S., we just demolished so much of what we had, and the skills, as David pointed out so nicely, the skills of people that can build these plants. And when you build and make things, then you can innovate. So, we're really losing that capacity, as we have such a collapse in our manufacturing base.

MR. WEST: Well, that is an interesting history and very problematic, in terms of what happened there. Nick has a question about -- can hospitals and other providers take any steps to ensure that they will have optimal quantities on-hand, during an emergency, or are they basically at the mercy of forces beyond their control?

MS. GIBSON: I think they should -- more hospitals should join Civica, or come up with another Civica, and use their combined purchasing power, basically, to create a new supply chain that's reliable, and full transparency on where the finished drug is made and the API is made. That'd be my answer to them.

MR. WEST: Okay. Okay. That sounds good. Lydia, of Bloomberg, wants to know, how will the international tax provisions of the White House's new infrastructure proposals affect supply

chains? Anyone have any thoughts on that? This is the first time I've ever seen a panel stumped by an audience question, so.

MS. GIBSON: It's too new in question.

MR. WEST: I assume by --

MS. GIBSON: It just happened recently, and -- yeah.

MR. WEST: I assume, by the tax provision, she's talking about the 15 percent minimum tax incentive.

MS. GIBSON: Okay. Oh, I see.

MR. WEST: So, do you see any consequences of that, in terms of supply chain issues? Okay, I guess we will pass on that question. Milt has a question. He wants to know, does the U.S. to place greater emphasis on the role of regional digital health and information exchanges, in shifting drug and medical supplies, among providers in a given region, or, basically, is there a tech solution to some of these supply chain problems? You know, can we use health information technologies, health information exchanges, as a way to shift supplies around, in order to come closer to having an efficient marketplace?

MS. GIBSON: I'll just jump in real quick. In a hearing, last year, on Capitol Hill, there was a professor, from Johns Hopkins, who described, before the pandemic, there were 200-300 drugs that Hopkins' hospital had in shortage. And what they do is they basically barter with other hospitals. Now, that's -- frankly, I think that's insane. Let's fix the problem with the market, so you don't have to create a whole new technology to fix a broken system. And it doesn't address the fact that you just don't have enough product. So, it's not enough of where it is and where it's not, but ensuring we have a stable market that is able to allocate product, as needed.

MR. SARDELLA: Yeah, and I'll add to that. In the research we've found, Darrell, I mean, there's very much advanced inventory management practices that are implemented and operated. Much like we've been talking about some of these medicines, which is small incredible margins, it is not economically feasible to have them sitting or stocked for multiyear availability, and so, they keep those stocks very thin because it's the only economical matter to continue to supply those stocks.

So, from one that which speaks to the question that was asked about earlier, about couldn't we just build up these supplies, such that we're prepared, they -- the management systems are

very advanced, but yet the margins are so thin, it's important that they keep the most minimal amount as possible. And secondly, the use of connected devices or connected systems, to be able to track and understand where we have gaps or shortages in certain areas, that absolutely would be a technology that'd be useful, maybe modernizing, as Rosemary has said, modernizing the trading. One could potentially have more insights as to where the products exist, where they don't, and how can quickly reallocate them, across the country. Connected healthcare is a very important area of focus that could alleviate some of those shortages.

MR. GAVARIS: Yeah, and then just, you know, my former life, I was the President of the third largest U.S. injectable manufacturing company, by volume. A lot of our time was spent on allocations with the shortages that occur in the injectable space. And I think, you know, it was paramount to us to try to get product to hospitals in need and understand how to create allocation systems. The hard part is products are flowing through distribution channels, multiple distributors.

You've got multiple manufacturers supplying these institutions, and so, getting back to what the root demand is for each of these institutions becomes difficult, right, in terms of getting that data, because you're looking at your slice of a pie, as a manufacturer or a given distributor, and so, being able to consolidate that data more in real-time, understand what inventories are, and where product's needed. Because there's human behavior by the procurement divisions of each of these hospitals, some of them are using those technologies to get ahead of the curve, to hoard, you know, products that they know are going on shortage, to protect their own interest, and then, you know, have leverage in these ordering things that go on behind the scenes.

So, you know, there's so many facets to it. It's very difficult. I think we've got to get to the point where there's more transparency about what's out there, what's needed, and the ability to be more flexible with the inventories we have, and, you know, the status of competitive manufacturing, right? There's such a worry about anti-competitiveness and collusion, within the space, that information doesn't flow. So, you know, the last ones to find out about a drug shortage is a competing manufacturer. Right, customers will know when somebody's out. A drug shortage will know. But then, the manufacturers find out later, through these third-party channels because we're not able to communicate. And so, I think that becomes another challenge. So, finding ways to get responsiveness to the competing manufacturers, so

they know to ramp up, and more information and transparency about inventory levels across the network, so that it flows, I think, are paramount there.

MR. WEST: Okay. Well, thank you very much. We will make that the closing comment. But I want to thank Tony, Rosemary, Spiro, David, and Ed, terrific comments, great insights, both into the nature of the problem, as well as possible solutions. And to our audience members, thank you very much for tuning in. At Brookings, we write regularly about these and other topics. So, feel free to check out writings at Brookings.edu. Thank you very much.

MR. GAVARIS: Thank you.

MR. THOMPSON: Thank you.

MR. PRICE: Thank you.

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