

MONTHLY UPDATE - NOVEMBER 2018

EMERGENCY PREPARATIONS DRAW HEIGHTENED INDUSTRY AND REGULATOR ATTENTION AS NATURAL AND MAN-MADE DISASTERS PROLIFERATE

Extreme weather events, political instability, and economic disruptions are prompting the pharmaceutical community to heighten its focus on emergency preparedness. The following four-part report focuses on conference presentations and discussions during 2018 that have made a significant contribution to understanding the increasing challenges that industry and regulators are now facing around the world and how they are being addressed.

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INTERNATIONAL PHARMACEUTICAL QUALITY provides in-depth coverage of emerging drug, biologic and combination product CMC and GMP issues and developments with a mission of helping advance and harmonize the quality regulatory process globally. Headquartered in Washington, D.C., IPQ is read by regulatory agencies, manufacturers, suppliers, consultants, law firms, and universities around the world.

IPQ tracks the industry/regulator dialogue at key international forums along with the developments, initiatives, regulations, guidances and standards in the quality regulatory arena to create a uniquely valuable resource for the intelligence gathering and knowledge management needs of the pharmaceutical community.

IPQ's "actionable intelligence" is particularly valuable for thought leaders and decision makers who need to have a deeper understanding of the issues and their context to help shape regulatory policy and develop implementation strategies. Subscriber support allows IPQ, in turn, to make an important contribution to the efforts of key non-profit associations and public service organizations engaged in addressing the increasingly complex manufacturing and regulatory challenges for medicines in the global context.

IPQ is published online, and the substantial archive at IPQpubs.com is easily searchable through its keyword search indexes. Links to documents referenced and cross-links to related previous IPQ coverage in the area are included, allowing readers to quickly dig as deeply into an issue and its context as needed.

IPQ's "**News Alerts**" provide links to the first few paragraphs of the stories newly posted online. Subscribers and license holders can click through to the full stories.

The "**Monthly Updates**" provide the stories that went online during the month in a print-friendly PDF format, and are an easy way for subscribers to keep up with the critical developments impacting the quality regulatory process worldwide. Included are "Updates in Brief" on recent CMC/GMP developments of note with links to the referenced documents and to our related in-depth analysis. Also included is an annotated listing of FDA drug GMP warning letters and recalls as well as EU GMP non-compliance statements posted during the month.

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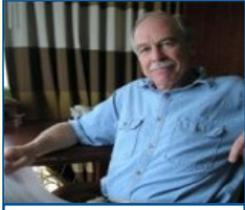


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Bill Paulson, Editor-in-Chief

NOTE FROM THE EDITOR-IN-CHIEF: The disruptions flowing from climatic, demographic, economic, and political forces at work around the world are prompting the pharmaceutical community to heighten its focus on emergency preparedness.

The November Monthly Update provides a four-part report on some of the conference presentations and discussions during 2018 that made a significant contribution to understanding the global challenges industry and regulators are now facing and what can be done to address them. With the impact of Hurricane Maria still very much in evidence, the 2018 IPEC-Americas/ExcipientFest conference – held in Puerto Rico in May – was particularly enlightening on these issues.

- In the first section, IPQ takes a look at the significant investments that Biogen and Baxter are making in data collection, mapping, analysis, and communication in the context of these global challenges, and the multiple benefits the companies are reporting in supply chain resiliency and security as well as planning and employee safety.
- The report then shifts to the regulator engagement in managing disasters. Provided are insights from FDA Emergency Operations Director Andrei Nabakowski on the agency’s substantive response to Hurricane Maria and other recent crises.
- Based on insights from internationally recognized author and analyst Dante Disparte, the third part offers a broader view of climatic, demographic, economic and political mega-trends and the planning that is called for from pharma and other global industries to prepare for the significant disruptions and risks they entail.
- The report concludes with a review of an expert panel discussion from ExcipientFest on the impact of a disaster like Hurricane Maria at the individual, company and government levels, and the lessons to be learned.

Among the developments during November highlighted in the “Updates in Brief” section is ICH’s November meeting in the US. It marked the first face-to-face meeting of ICH’s expanded Management Committee, which now includes representatives from the agencies of Singapore, Korea, and China and from the associations BIO and IGBA. ICH now has 16 members and 28 observers. [See IPQ [September 6, 2018](#) for an in-depth review of how ICH is evolving.]

Also of note in the international arena was the inclusion of five more EU member states in the US-EU MRA, with the capability assessment of all EU inspectorates by the US expected to be completed by July 2019.

Breaking the normal pattern of a rough equivalence in US vs. foreign drug GMP warning letters, all of the letters posted by FDA during November addressed issues at US facilities. Two of these addressed compounding and four focused on finished dose operations. Among the latter was a warning letter issued in November to Mylan following an inspection at its Morgantown, West Virginia facility that concluded in April. Cleaning, OOS investigations, and change management were focal points of concern.

EMA posted two GMP non-compliance reports – both regarded API facilities in China. One of these was a maker of heparin, and the other, of sterile B-lactam.

FDA listed 32 drug recalls during November, almost a third (10) of which involved microbial contamination or lack of sterility assurance. Two of these – involving an oral spray and eye drops, respectively – were rated Class I as posing a serious health risk. The third Class I recall was of dietary capsules with unapproved drug ingredients.

PART I

Biogen and Baxter among Pharma Companies Investing More in Disaster Preparation

Pharmaceutical companies that are making significant investments in data collection, mapping, analysis, and communication are reporting multiple benefits in the areas of resiliency and security of their supply chains, as well as planning and employee safety.

Biogen is an early adopter of a comprehensive data management system that tracks virtually every aspect of the organization's business activity.

At the 2018 ExcipientFest conference held in San Juan, Puerto Rico in early May, Biogen's Global Product and Supply Chain Security Director Lee Spach and Regulatory Intelligence & Pharmacopoeial Affairs Head Janeen Skutnik-Wilkinson gave a presentation on the company's intensive supply chain tracking/security system and how it is used to ensure unbroken supply lines during natural disasters, terrorist attacks, and geopolitical disruptions.

The timing and location of ExcipientFest – in the wake of Hurricane Maria, which had devastated the island the previous September – gave added weight to Spach's and Skutnik-Wilkinson's presentation. They focused on Biogen's successful handling of operations both during and after Maria, as well as Hurricanes Harvey and Irma and the Mexico City earthquake, all of which occurred within a few weeks of each other. *[The full presentation by Spach and Skutnik-Wilkinson is provided on pp. 6-18.]*

Monitoring Center Deploys the Resilinc System

In 2016, Biogen began utilizing the Resilinc online data management system, which, Spach explained, had been developed at MIT in 2005 in response to a supply chain incident at General Motors.

After entering into the system information about virtually every component of their 'direct spend' purchasing – "from a filter to an excipient to an API, to whatever it may be, even printed components for label packaging" – the company went further, asking their suppliers, whom Spach referred to as "partners," for information about their own suppliers in turn.

Biogen established a "Global Security Operations Center" to manage the data, Spach explained. The center was set up

to monitor internal operations, as well – everything from humidity levels to location of employees at all of Biogen's facilities around the world.

The result was "visibility," not only of multiple tiers of vendors for the company's own manufacturing processes, but more importantly, for the company's contract manufacturers, as well. "This tool has allowed us to gain visibility," Spach noted, "because it is hard to protect what you cannot see. It is hard to predict what you cannot see."

Skutnik-Wilkinson added that the system even monitors FDA 483s and warning letters – "anything that could impact us from a quality perspective."

With access to this information, Spach continued, the company established a cross-functional team – engaging people from "quality, supply chain quality, logistics, site manufacturing, external manufacturing, procurement, finance" to posit scenarios that might impact the company's operations.

The System at Work in Disasters

Spach and Skutnik-Wilkinson then focused on the system's use during Hurricane Maria. Biogen's access to data provided a comprehensive picture of operations and allowed the company to avoid supply interruptions.

Among the "lessons learned" from Biogen's experience with Maria, they explained, was the value of the system in: • developing standard operating procedures for a variety of "what if" scenarios • evaluating the company's dependency on custom-made rather than "off the shelf" components, and • managing emergency communications, both internally and publicly.

"I think the biggest one is streamlined communication," said Spach. "I am an ex-military guy and I can tell you the more you can control communication and can control the spin, as I call it – the swirl – the better off you are."

The 2017 Mexico City earthquake offered another test of Biogen's system. Spach and Skutnik-Wilkinson provided a case study of how the company analyzed and managed the earthquake's impact on their operations, and how they further integrated lessons learned from the experience into emergency planning as well as day-to-day operations.

How about Confidentiality?

During the Q&A that followed the presentation, several questions addressed issues around personal privacy and company confidentiality.

When asked if Biogen gets “pushback” from employees who do not necessarily want their whereabouts known at all times, Spach responded that the tracking and communication system has proven itself so useful that employees appreciate its value, and some even utilize the system for their private vacation travel. He cited examples of terrorist incidents around the world when the company was able to warn an employee to keep out of harm’s way.

Another question focused on confidentiality issues when gathering information about Tier 1, Tier 2 and Tier 3 suppliers, since few companies generally want to reveal their sources.

Skutnik-Wilkinson responded that only about 5% of suppliers give some pushback – usually only those that have a nominal relationship with Biogen. Most readily cooperate when they understand that there is mutual benefit.

“Through education, webinars etc., we explain to them that there is a benefit to them, as well,” she said. “For example, when I get an impact notification that a 483 or warning letter has been issued, [the system] also sends those details to the individual supplier that could be potentially affected as part of that food chain.”

A final question regarded the use of non-disclosure agreements (NDAs).

Spach replied that Biogen’s process for getting cooperation from suppliers involves a letter of introduction and explanation, and that Biogen has never been asked to provide NDAs. However, he noted that he had recently been hearing about other companies that were trying to implement the Biogen model that had been getting requests for NDAs from some of their suppliers.

Baxter Highlights Benefits of Preparedness

Providing a complement to Biogen’s emergency preparation and response strategies, Baxter Operations Strategy and External Contract Manufacturing VP Chris Jones, speaking in Washington, DC at the 2018 PDA/FDA Joint Regulatory Conference in September, emphasized the importance of building good relationships with local service providers and suppliers for everything from fuel oil for backup generators to provisions for the company cafeteria.

Like Biogen, Baxter has also implemented a commercial service that keeps track and reports on global threats – from earthquakes to changes in company ownership worldwide.

Baxter has implemented a “threat management system” to keep track and make sense of the vast amount of data the service generates, ranking the information into three broad categories – green, orange, and red – corresponding to urgency and relevance.

The company has also implemented an emergency training program so that managers and employees can regularly rehearse their responses to a variety of stipulated scenarios. Integral to their emergency procedures is a central command control center to manage any crisis.

Lessons Were Learned from Maria

Jones pointed out several key “lessons learned” from the company’s experience with Maria, emphasizing that taking care of employees’ needs is paramount – from ensuring the basic necessities of housing, food, and transportation, to having enough cash on hand to pay them when electronic systems fail.

Redundancy of systems and supplies was a key factor. Instead of just enough emergency generators to maintain power, Jones noted that an extra one is needed so any machine could be taken off line and serviced as needed in an extended outage, like the three months they were without external power in Puerto Rico after Maria.

Another key factor, Jones explained, was collaboration with local, state, and federal agencies.

During and after Maria, for example, the company worked closely with the FDA, getting quick approval for alternate sources of ingredients in order to maintain the flow of pharmaceutical products to patients – and with local municipalities to get roads cleared so employees and materials could get in and out. Assistance was mutual, he observed, with Baxter providing resources and equipment to assist the town in its recovery efforts as well.

In the wake of Maria, Baxter set up a “disaster relief fund” for its employees worldwide, explained Jones, so that when another disaster strikes there will be a resource those affected by it can draw on to rebuild their lives.

Jones also touched on the timing of plant maintenance windows to ensure that inventories were not depleted when entering hurricane season. *[Jones’ full presentation is provided on pp. 19-25.]*

Set Priorities in Advance to Prepare for System Failures

Even with three redundant communications systems (fiber links, microwave, and satellite), communication was spotty, so Baxter staff quickly learned that when first making contact it was essential to follow standard protocols and structured lists of “need to know” items. They also learned to prepare standard supply lists in advance so that crucial

communication time did not have to be taken up going over what should be obvious necessities like baby formula, diapers, water, food, batteries, etc.

Finally, recognizing the vulnerability of relying on the cloud and electronic systems for managing mission-critical data, Jones noted that part of the company’s checklist in the days leading up to a predicted disruption is to get critical data printed on paper and to ensure that employees knew how to run the computations manually.

LEE SPACH AND JANEEN SKUTNIK-WILKINSON ON BIOGEN’S SUPPLY CHAIN TRACKING/SECURITY SYSTEM



At the 2018 ExcipientFest conference in San Juan, Puerto Rico in May, Biogen Global Product and Supply Chain Security Director Lee Spach and Regulatory Intelligence & Pharmacopoeial Affairs Head Janeen Skutnik-Wilkinson gave a presentation on Biogen’s intensive supply chain tracking/security system and how it is being used to ensure unbroken supply lines during natural disasters, terrorist attacks, and geopolitical disruptions. Formatting changes and other minor edits have been made by IPQ for clarity and readability. The normal disclaimer that the presentation represents the views of the speaker and not necessarily that of his/her organization is not included.

[Spach] Today we are going to tag team a little bit with my colleague, Janeen, whom you all know probably very well, to fill in some of the blanks.... I am going to let her tie in to my presentation today some of the things specific to this particular group and this particular conference that we are at.

First and foremost, I have three main responsibilities at Biogen: • One is supply chain resiliency • The second one is... supply chain security, meaning the products that we manufacture, whether it be raw materials inbound, to finished goods at the patient’s level – making sure the patients get the product they are supposed to get. So, counterfeiting, theft, diversion all that falls under me. • And then I have a product protection group, which is responsible for technologies at the product or packaging level, etc. that we can use to identify and make sure that our products are authentic that the patients are receiving.

But today, for the purpose of this, what I am going to talk about is actually our resiliency program, and a little bit about how we managed during Hurricane Harvey, Hurricane Irma, Hurricane Maria and something you probably don’t remember, the Mexico City earthquake – so, talking about the journey that we have been all through about 2-1/2 years now and where we have come with that.

Janeen, anything you want to add?

[Skutnik-Wilkinson] Yes, one of the things, too, is that we are going to try and connect in some of the things that specifically impact excipients. So, as Lee starts going through different things, we are going to talk a little bit about how some of these tools actually can be used with things like those great quality risk assessments that we all have to do for excipients.

Everyone is on that path. We all have our risk assessments. So, there are tools that we have in place – and Lee will talk more specifically about what these tools are. But one of the things that we have learned is that we can actually take this information and pull it into our risk assessment.

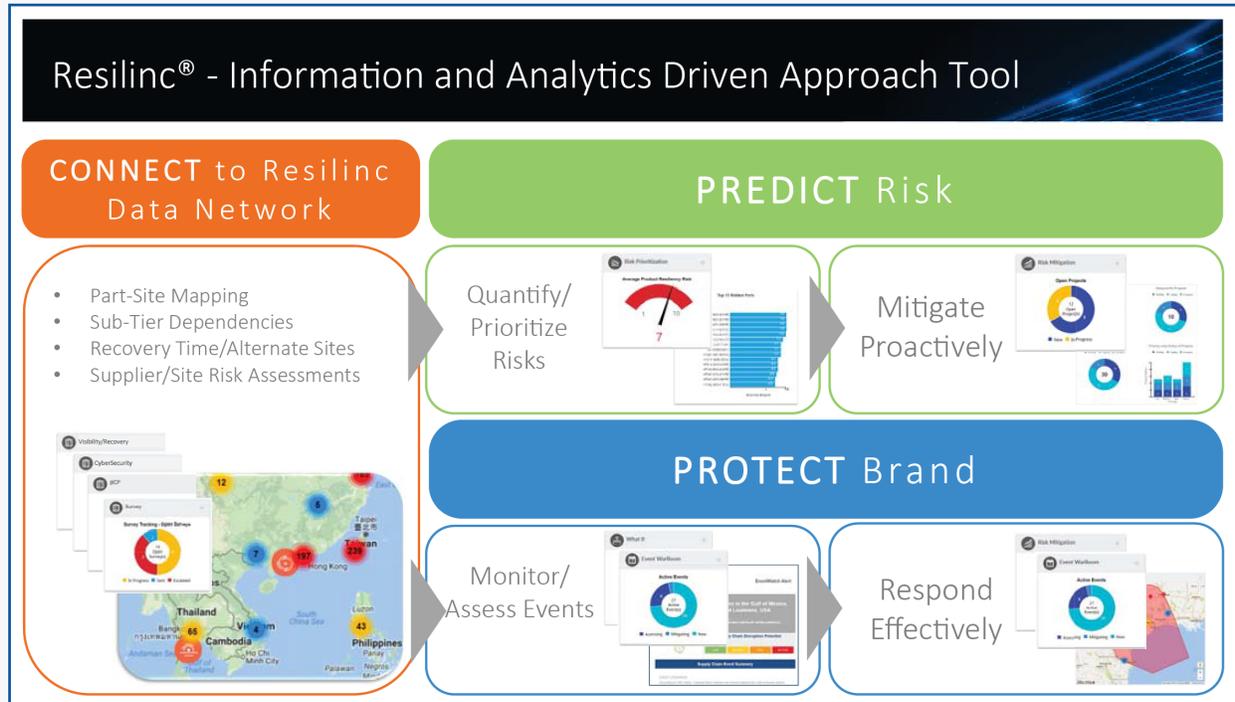
So there is simply business continuity. There is information about where our suppliers are in the world, which then helps us better understand, ‘okay are these areas that are at risk for various different events.’ For years right after heparin we were talking about, ‘How the heck do we get this information and how do we use it?’

What Lee is going to talk about it is basically things that help us do that really quickly in real time without a lot of extra investment in time and people to pull all the data together for us....

Collecting and Analyzing Data For Supply Chain Integrity

The Resilinc Tool

[Spach] First and foremost I am not going to do an advertisement for any particular tool other than this happens to be the tool that we use – that we identified through an RFP process a couple of years ago for helping us build our resiliency platform. So we will actually talk about a tool called Resilinc.



Resilinc was born out of a case study at MIT back in 2005 based on an incident that happened with General Motors – the incident in Japan – and how 16 weeks later all of their manufacturing sites globally went offline because of a 50¢ air sensor that every vehicle of every line that they produced utilized.

As a practitioner of supply chain for the last 15 years, I wish this tool existed in my life when I was in the apparel industry dealing with just-in-time deliveries and dealing with everything from tsunamis wiping out ports, to the plant fire that burned down the plant somewhere in Asia that you are dependent upon for raw material, to ‘Oh, the truck got stolen in some hostile environment somewhere,’ and your raw material never gets to you, or your finished goods never get somewhere.

This tool has allowed us to gain visibility, because it is hard to protect what you cannot see. It is hard to predict what you cannot see. Now, I am not saying that the tool, in and of itself, answers all questions for all companies. It is not a ‘One mechanism finishes the supply chain risk’ for you, but this tool allows us to connect, predict, and protect.

Basically it is an online database in the Cloud where we store at the part level Biogen ‘direct spend.’ So, we know every item that Biogen spends: everything from a filter to an excipient to an API, to whatever it may be, even printed components for label packaging. We part number those into the system with who their suppliers are. That goes up in the database. Then we survey those partners. We reach out to our vendors, our partners, to say, ‘Okay we know that for Biogen, you make part X, but what is it you are buying, who are you buying from that goes into making part X?’

Understanding the Full Dimensions of the Supply Chain

So we start getting tier 2, tier 3, tier 4 visibility up the supply chain from our supplier base. More importantly, we do the same thing with our contract manufacturing operations. So, we go to our CMOs and we say, ‘We know you make fill finish for product family X, and because of that we want to know what parts you have to go in to this product family as well.’ And then we start surveying them and go on up the chain as well.

So, you start gaining visibility for sole source or single source of the areas that you identify that you may not have even thought were sole sourced or single sourced. Because a lot of companies will say, 'We buy this from five different vendors.' Yeah, but who do those five buy from? 'Well, they buy from two.' But who do those two buy from? Well, one person that makes it in some remote place you have never heard of before. It just is what it is. It's the nature of the business.

I think also what happens a lot of times is parts that are spec'd specifically for your organization – and I will talk a little bit about that as we go through the Hurricane Maria thing in a minute. But anyway, so we map the supply lines and start understanding sub-tier dependencies. We start understanding then recovery times from the partners from where we do map – when we mapped, for example, our partners on the island of Puerto Rico.

Biogen does not make anything in Puerto Rico. We do not have a site here. We do not have CMO capabilities here. But we do have tier 1 and tier 2 suppliers, and tier 3 suppliers. Two years ago, we did not even know they were in the Puerto Rico – that our specific products were coming from the island.

Fortunately, by building up a supply chain map and building this visibility, it allows us to see better, which then, of course, gives us the ability to predict. I will talk a little bit how we used this mechanism to predict. And then from that we can mitigate. And then we can get a monitor and move along our daily normal operations.

So first and foremost, we are structured a little bit differently than a lot of pharmaceutical companies when it comes to supply chain resiliency. I actually sit in our global security organization. I do not actually sit up on a supply chain anymore. I used to be in supply chain group, but when I took this role to build this program, they pulled me out of that.

And the reason is because our security organization at Biogen is probably the only 24/7 group that actually is manned where they are monitoring things. Our security group is monitoring not only our assets at site level, but they are monitoring employees, they are monitoring travelers, we are monitoring all sorts of things.

It just makes sense for this program to sit up on a security organization, because it looks holistically across all of Biogen, and not just one of those specific line function areas, or within manufacturing as opposed to commercial, or commercial rather than clinical, etc. So we get a broad view. That is why we built this program out underneath the global security group.

The Global Security Operations Center

I will talk a little bit about how we leverage what is called our GSOC, which is our Global Security Operations Center...because I am building up to how we manage the pieces.

Our GSOC is monitoring internally for Biogen – everything from our cold chain in our own facilities, monitoring humidity levels, monitoring access control for all our doors globally around the world at our different sites, and our offices, monitoring where our employees are: we monitor travellers when they are on move, and we issue a wide variety of alerts and crisis management.

Our entire crisis management team is dedicated just towards Biogen business continuity and also our travellers, etc., as they are moving around. Keep that in mind because we tie into that, and I will show you how we do that.

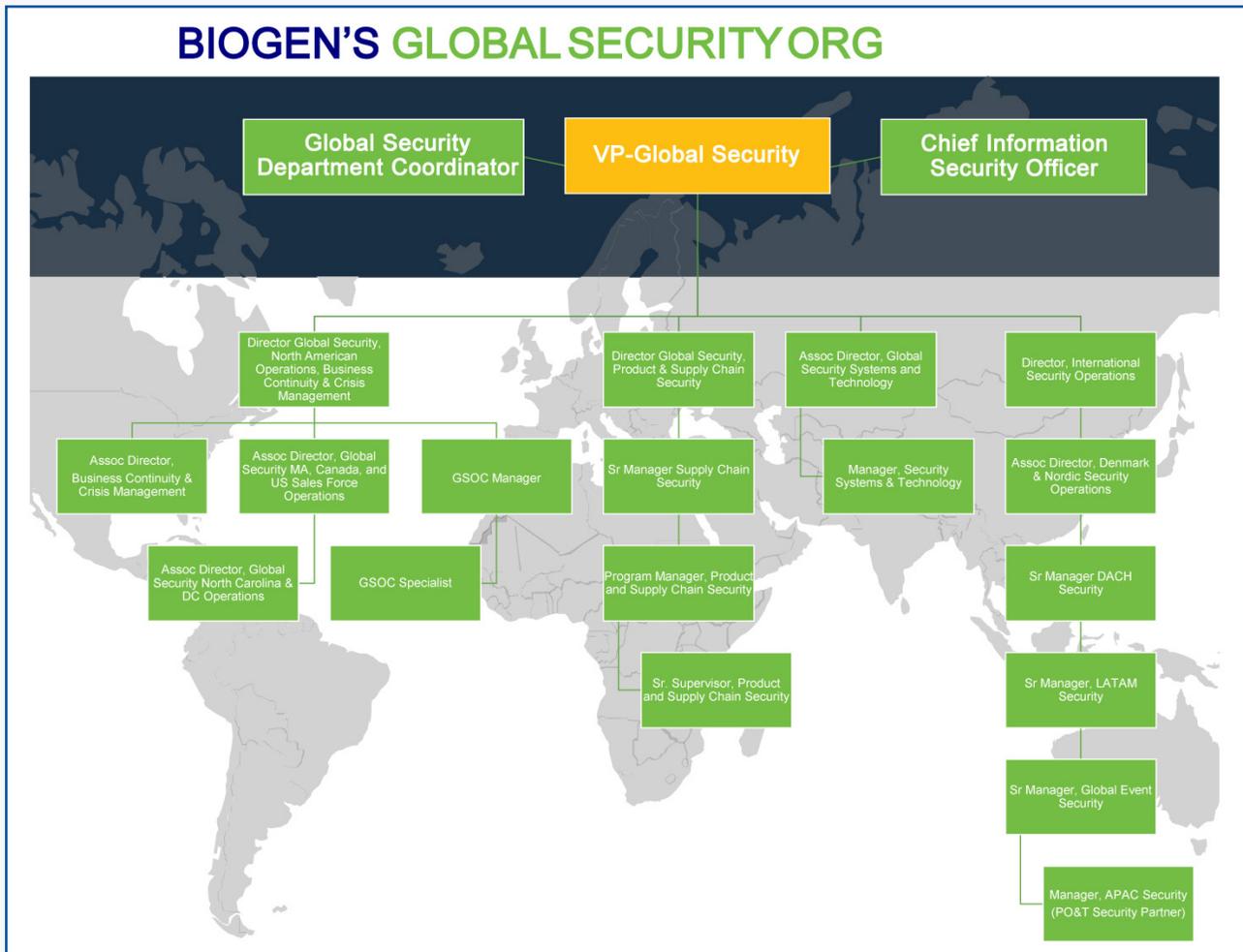
The other piece that we hear is where we run the Resilinc Event War Room. We have built an internal process that said, 'We have this tool. We have mapped our supply chain. We now have visibility to items that we have not seen before within the supply chain. Now we need to build a robust mechanism to be able to predict and look at events that may occur around the world - geopolitical terrorist activity, hurricanes...'

That is a good one! An earthquake that happens and we immediately know within a couple of minutes, based on intelligence, where that is going on. We can geofence quickly and say 'Do we have a site there? And do we have people, employees, assets, suppliers there?'

So, from that we started being able to build predictive, 'what if' scenario capability. It allows us to see things, hopefully, before they happen.

[Skutnik] It is one of the cooler things. If you guys remember when we first started dealing with supply chain after heparin: One of things that Lee and I kept trying to convince people was the biggest risk was not necessarily the company that you buy tens of thousands of kilos from. It can be that one company that has that critical excipient.

This process allows us to drill down and get that information. So, without adding layers of people and having a 100 different people sit in a room and say, 'Okay let's start culling through this information,' it allows you to then look at those segments and say, 'What if something happens in this region?' Because that is such a critical part. It helps you to be better prepared for those instances and I know it is something that certainly we have talked about a lot since the heparin incident.



Cross-Functional Teams, Collaboration, and Communication

[Spach] This in a nutshell is how we defined it: We use our GSOC as our central point. The tool is, as I said, in the cloud. We have a cross-functional team that sits over here that is cross-functional across Janeen's and some other team: for example, quality, supply chain quality, logistics, site manufacturing, external manufacturing, procurement, finance. Because we have to look at impact, we could run revenue data through here, as well.

You can also attach it to product family, attach product family to revenue globally, and you can look, this 50¢ filter – for lack of a better example – how it flows through this process, flows to this product family. If that node goes offline or that part comes out, its impact of having many billions of dollars of revenue in that particular product family could be at risk, depending on what the product is.

So we use this resiliency team down here to manage and run the actual program. Early on when we first started with Resilinc and started building out our map, we did everything manually. We went into Oracle, we would go into other ERP systems, pull data out, manually manipulate it and then push it into the Resilinc system, because they have their own platform that they operate on.

Now, fortunately, 2-1/2 years later, we are finishing up on IT integration, where our data will come straight from Oracle and other ERP and VRP systems, and push straight into them. There is a validation process that we put in place and then from there the data will go live right into their system. So we do not always have to come back to these manual refreshes every 3 months, 6 months, something like that.

This team down here is a lab working team. And the key to success of our resiliency program is cross-functional support and buy-in. It is critical. As a supply chain professional, I could not have done what we have done, building up this resiliency program and having the visibility we have, without the buy-in of other line functions within the organization and without someone to be committed to be a champion from each of those line functions, like Janeen for example.

If it was not for her commitment to the program, to the team and say 'Hey, this is an area that we actually see value added – if I could get information from this, I could do something in my job that makes my job a little easier.' And that is a hard sell. It is also a hard sell for a tool like this because a lot of times you go to see your leadership level and say, 'What is my ROI? I want to know the ROI on this.'

The ROI on this isn't that you are going to necessarily save a pile of money. More than likely, it is going to be cost avoidance. And luckily this case study for us for Hurricane Maria became a big win for us as far as cost avoidance because of the amount of time and effort that we personally had spent as a company worrying about Hurricane Maria – and I am not downplaying the effects of this because other companies were devastated by it, and of course the whole island was.

But for us the impact was minimal because we had the process and the procedures in place to predict what potentially could be a major impact and then take action before the impact actually even occurred.

Now, all the time you cannot do that. So we have this team that is daily engaged with your license system as well – like Janeen for example has her own credentials, so she can get into the system and see that there is something she wants to look at as far as supply chain or certain node or whatever. She also gets access to intelligence.

Resilinc, in addition to being a tool, the service that they provide is called 'event watch.' They are looking around the world and they are looking at supply chain impact events only. So, they are looking at 483s and warning letters. They are looking at labor strikes in regions in China, or wherever the case may be, or they are looking at geopolitical instabilities in certain regions. They are pushing out intelligence based on that. So Janeen, for example, gets that intelligence and she can take action for her job in our supply chain for protection of that. You want to have a look at that?

[Skutnik] Yes, so we are looking at things like 483s – anything that could impact us from a quality perspective – and then bringing that in and making sure that they were aware of it, because we have got commitments to FDA on drug shortages where we have to notify.

This allows us to have that information really early on so that we can do a really quick assessment to determine if our patients are going to be impacted, which is so important – not just because we have that commitment, but it allows us to then determine if we are going to have any issues where we really need to figure out what we need to do to make sure that our patients are being covered with their medicines.

The other thing that I will mention is – for those who attended my integrity workshop yesterday – we talked a little bit about the Cloud. And so the cloud here that we are using is compliant with data integrity expectations, and you will see that with a lot of the cloud services they have already built that in. So if your company is hedging about 'do we go in that direction?' there are a lot of Cloud services that have built in those requirements, which again for quality regulatory professionals is something really important for us to think about.

[Spach] Yes, a lot of these requirements, actually – like this particular tool that we use – is compliant because this particular company does a lot of business with the Department of Defense, as well. That is always a good indication that, 'Hey, if you start at this point, you probably have a good likelihood that you have a pretty solid data integrity mechanisms in place.'

So, anyway, the resiliency team is always functioning in and outside of crisis, and are using the tool and information coming from the tool on a daily basis in various jobs around Biogen. What we just see is the process we have for when an event occurs. So, as I said, our GSOC, which is our Global Security Operation Center, they have this tool open right now.

They are monitoring intelligence going around the world from crowdsourcing on Twitter to all sorts of stuff. So anytime anything occurs, again they can geofence it. By going to this tool, they can geofence that area and say, 'This might be what the impact is.'

'What-if' Scenarios

What is really cool is when you run these 'what if' scenarios. So take the hurricanes and the earthquake. The hurricanes we knew ahead of time based on the news that hurricanes would come and they would potentially have impact. So anyway what happens is they run the what-if scenarios in the GSOC in real time as events are occurring. They are also analyzing Biogen assets etc.

They feed that to me and my team. We have a process in place that says, 'Hey, do we need to stand up a War Room?' And the War Room sometimes is virtual, sometimes it's just on Skype, sometimes it is actually physically in a conference room depending on what the impact may be.

The Hurricane Maria Experience

When Maria was inbound after Harvey and Hurricane Irma came along, we needed to stand up in a conference room. I was losing my mind trying to figure out which one are we talking about today? Are we talking about the impact to Florida or Texas or we are talking about the impact to the Caribbean as they were coming through?

We stood up a war room in a conference room, brought in all the people from Resiliency team, pooled up the dashboards within the tool itself and said, 'Okay, we have identified that if there is a catastrophic damage done to the island of Puerto Rico, we have X number of suppliers that manufacture products for us on the island, and these particular items are what we get from those manufacturing nodes that are located on the island of Puerto Rico. We had dozens of total items that Biogen consumes in our manufacturing plants even though we do not make anything here – about three dozen items that were made on the island of Puerto Rico.'

When we got further into the data, we said, 'Wait a second, some of these 36 items – let's see if we do have other parts that we can interchange. Do we have something else qualified? What does our inventory position look like? What does our consumption look like over the next 6 months, 12 months?'

Lessons Learned

So we have to think that far in advance. We were looking at inventory positions, looking at our procurement schedule, looking at: 'Can we talk to several of our partners and see if they are going to do level loading in other facilities – the ability to make the product for someone else?'

We worked through a bunch of different scenarios, and at the end of the day we ended up with a small group of items that were Biogen spec'd – made just for [us]. In other words, we had painted ourselves into a corner when we designed some items that we probably should have used off-the-shelf solutions for, which was a lesson learned.

It was 'Why did we make these particular items spec'd for us? We didn't need to. There are other off-the-shelf solutions that were just as good that we could utilize.' So we did end up kicking off a secondary sourcing activity and then we pulled cords in purchasing.

But, again, we knew a week in advance, and we were playing 'low probability/high impact' scenarios. It is low probability that it could come across the island, but if it does, it is a category 5 that could be devastatingly high impact. So again we worked through a lot of scenarios of what to do and then already started taking mitigation actions against that.

This just shows pretty much what we did. This is actually a screenshot I took from the tool. We can screenshot an impact area with a geofence and from that run some analytics and that can tell you what companies are in that box and what items are connected to those companies in that box, etc.

Again, we can do very robust data. So we avoided stock-outs of certain drug substance bags that we use for freezing biologic material. We identified several that were made only to our specs and initiated a dual sourcing project out of it.

We take this all the way through the supply chain, not just in bits and pieces. One of the things that we also did was we started identifying how much product we have coming into Puerto Rico as far as to the patients – in other words, from our facilities outbound. And we said, ‘OK, we need to slow this down.’

We made sure our commercial organization worked with our partners here to find out how much pharmaceutical products were on the island and how long that supply would last – as opposed to us trying to push it up through right after the Hurricane came, when everybody was in turmoil to know what was going on and you could not get stuff in and out of ports, and things like that.

We controlled our flow out of the US into Puerto Rico intentionally. And then of course we helped find some lost shipments from some product that was inbound for a sister company of ours – a company we spun out a little over two years ago. We were actually still monitoring their product over time, and they had moved some product. It was en route to Puerto Rico before we could stop it, and it actually had gone lost, and we had to find that. So we utilized this tool and other mechanisms to be able to find them.

HURRICANE MARIA RISK AVOIDANCE



Avoided potential stock out of certain drug substance bags across multiple products



Team identified several bags that are made to Biogen only specs; initiated dual sourcing project



Limited product flow out of US to PR to ensure delivery



Team assisted in the successful interception of “lost” shipments from USA to PR.



Hurricane Maria Takeaways

What were some of the big takeaways we had? Some of these big takeaways were:

- Obviously #1, that you could do proactive assessment, identify where the sites are, where the products are coming from, where the raw materials were at, etc., and run some assessments on those. The Resilinc tool happens to be a tool that works very well for us in conjunction with SOPs and processes that we put in place.
- We made some decisions early on to ensure extra capacity, which is why we pulled forward some purchasing. Again, we were moving around some of our purchasing decisions a week before Maria actually hit landfall.
- Third was utilizing the risk intelligence and utilizing our SOPs and our crisis management teams to leverage and push the data up.
- I think the biggest one is streamlined communication. I am an ex-military guy and I can tell you if you can control communication and can control the spin, as I call it – the swirl – the better off you are.

HURRICANE MARIA TAKEAWAYS



You want to control the facts and data and information, and don't want everybody communicating outward and upward at the same time. Because then – especially senior leadership – they get something from their line function that looks different than they got from somewhere else. Now they are going to ask you a bunch of questions, and you spend all of your time in minutiae answering questions and worrying about 'how am I going to get the story straight,' as opposed to focusing on solving the problem.

One of the SOPs that we have in place is a very streamlined mechanism for how the supply chain resiliency team communicates up and out. Of course, each incident could be different. I mean a hurricane is going to be a little bit different of a mechanism for us to communicate up and out in our organization, as opposed to if there is a labor strike and it is impacting the certain area in a region of the world. But anyway, that is a key one – to make sure you have got good streamlined communication.

[Skutnik-Wilkinson] And I think too, from my perspective, one of the key things we are having in processes like this is we are often called upon by FDA and other agencies to talk about what do we think the impact is to an excipient or to products.

Being able to have some of this information allows us really very quickly to work with the FDA and other agencies to help them and start going in the right direction with good information as opposed to speculation and scrambling where people are like, 'I don't know what to do. I don't know what the impact area is,' and sometimes it might take us a few days to find out. Things like this will help us bring out the FDA and other agencies to react quickly where they need to.

The Mexico City Earthquake Experience

[Spach] In the middle of Hurricane Maria, Irma, and Harvey we had the Mexico City earthquake. Fortunately, for us again, this is one of the reasons why I set the stage a little earlier with the fact that we are a little bit different at Biogen in the sense that we put our intelligence gathering mechanism in that process in our security operations center.

Again we are monitoring 24/7 things that are occurring around the world. So while we were solely focused on what we are going to do with these three hurricanes and how do we minimize impact, you had a real life situation occur that we likely would have missed because we were so head-down focused along with the rest of the team on what is going on.

Meanwhile, we had Mexico City pop up. Here is an earthquake again. We have intelligence mechanisms where we use crowdsourcing from Twitter and other social media. So we know a lot of times, especially in something like an earthquake, long before CNN or Fox News will start carrying it.



MEXICO CITY EARTHQUAKE IDENTIFYING QUALIFIED ALTERNATES

Event WarRoom and What-If tool

- Identified vials used in US manufacturing ops
- Distributor and 3PL warehouses that sell to Mexican market
- Clinical sites and supply movement in surrounding Mexico City areas

Qualified alternate site outside impact region

- › Worked with suppliers to evaluate impact and viability of secondary inventory warehouses.

But I think we are very unique at Biogen in the capability that we have. What these guys were able to do was go into the tool, geofence an area around the impact zone and say, 'okay, what is here?' And we quickly identified that we did have a site within Mexico City area that manufactures vials for us. Luckily, through our SOP the communication went to the relationship owner that owns the relationship to that commodity.

That commodity manager reached out to the supplier and said, 'hey, we know that you are inside the impact area where the earthquake just occurred. Are you guys going to be able to still continue to supply this material, or what is the case?' And they started gathering intelligence really from the source at the site level of what was really going on.

Same thing going downstream the other way. So for Biogen, for example, we sell product into Mexico – not through the Biogen footprint, but we use a distributor to sell for us there. So we are one step removed. But we know where their warehouses are because we have mapped them. So we know that even though they are our partner, we had material in the impact zone.

Again, we have an SOP that says, 'going this way downstream – down channel – reach out to the owner of that relationship and find out hey, do they still have inventory, or are we are going to have to worry about replacing inventory sooner than our normal replacement cycle?' Fortunately for us there was no impact on many of them.

But the one that was most insightful to us was clinical trial sites and supply movements. We did not have, and we still do not have, clinical information in this system. And it was not because we did not want to ever get there. It is just that we were focusing all of our time and energy on the commercial supply chain.

So luckily, we do have a clinical person that sits on the resiliency team, and he said 'Look, I know this system and I can go offline and I can go into our own system to find what we have in Mexico City.' Sure enough, we had several clinical trial sites that were impacted. There were some slow-moving materials. I think a couple of patients may have missed the dosing on the clinical trial by a day or two. They had to make some changes, and all that was fine.

But wouldn't it have been nice if we could have seen that within a matter of minutes, as opposed to taking two to three days, to be able to do that through a manual process? This is a screenshot of our current global view of what we had in the system, and it just looks like a lot of numbers, right? And it is.

Right here in the United States there are 550 some nodes. Now it does not mean those are all Biogen nodes. Those could be CMOs, tier 1 suppliers, tier 2 suppliers, could be CMO tier 1, tier 2 suppliers, etc. So it is amazing when you think you have a pretty small supply chain, how big your supply chain really is once you start building this matrix of looking out through the spider web to all the different nodes, etc.

We are in the process of mapping all the clinical trial sites and studies by number. We have figured out the way in the system to do that. So now we can go in and run a 'what-if' in the region and say, 'Hey, what do we have here for the clinical trial? What clinical trial is it?' So that will be good moving forward.

Expanding Use in the Future

Mapping the Clinical Trials

What is interesting from that is once we have turned the clinical guys on to the value, and they start seeing after the hurricane and stuff, 'What can we get from having the supply chain map like this?' Then we take that further upstream to R&D and now we get people coming to us saying, 'wait a second. Do you think we can get predictive data out of here for when we actually go to develop a clinical trial?'

And we ask, 'Well what do you mean by that?' 'Well, there might be certain locations we do not want to do a clinical trial in because they are at high risk. It might be because there is a high risk of hurricane, because there is a high risk of geopolitical instability, etc..' If you have it mapped, you can draw a circle around an area. Now you can start at least having some data to look at to help make some of those decisions.

Maybe we have too many clinical trials at one location. Geographically, maybe we want to disperse that a bit more and minimize some of the potential risk of what could happen in the future. So they are going to start doing that. We can monitor our clinical trial sites just like we do our supply chain nodes. There is impact again from a potential risk.

And then we could utilize risk 'score.' There are various mechanisms in the systems that allow us to risk-rank by product family or by product site or by partner. There is a whole different multitude of leverage we can pull. 2-1/2 years into it we are just starting to understand that piece of it – in other words, what that really means, what the risk score really means, and how we want to risk-rank certain items for Biogen because it is totally customizable.

We did not want to jump in too fast to start ranking our supply chain before we actually understood what the data was and what we are going to see. That is why it is taking so long to get there. But we are now starting to put risk scores in place based on different regions, and based on different partners, and maybe even around their financial stability, etc.

The big thing is being able to future-plan where clinical trials need to be. That was something we did not even think of 2-1/2 years ago when we started working with mapping our supply chain and seeing what is going on – definitely a good thing.

[Skutnik-Wilkinson] And I will just add something about the risk scores. When you think about our quality risk assessment, if you have hardened your supply chain you already know what the risk scores are for that region, for the suppliers from a business perspective. Then that makes your overall risk assessment so much simpler because then you really just take that information you have from your audit and from your experience. You really then can target your quality people on that quality piece because you know the quality of the information you are getting about this – its continuity and its geopolitical risks.

Playbooks for Nearly Every Situation

[Spach] This tool is only to use the playbooks you have in place, to utilize them in process. So again we were moving first to put this thing in place and start utilizing. It was very relationship driven. I happened to know who the right person was to go talk to you in a certain line function, or who might have pieces of information, but you cannot run a business that way.

I may not be here tomorrow. Because of that we went back and said, 'we need to design real logs, living document playbooks that show what this team needs to do – whether it is quality or whether it is clinical, whether it is logistics, or whoever is a part of the resiliency team, where the what-if scenario is going to impact. Again, depending on the event, you could have a different impact to different parts of Biogen's organizations.'

We build these playbooks with that in mind. This worked very well for us with the hurricanes because we knew something was going to happen. We did not know the magnitude of it, so we were running all sorts of scenarios: ‘What if it does not do anything’ – all the way to ‘What if it completely wipes out all manufacturing on the island.’ No one could have actually thought we could have predicted that. We did not predict it. We just ran the scenario on it.

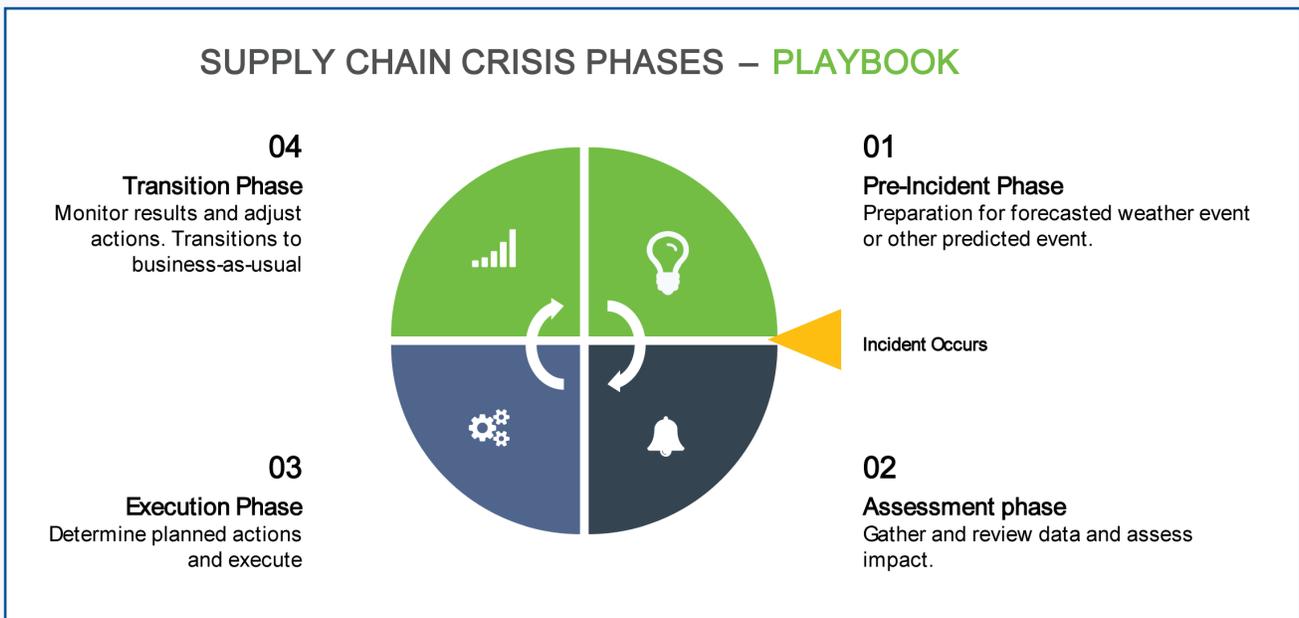
The cool thing about being able to run the what-if scenarios is we can go into the tool and then say, ‘what if we lose part number 1, 2, 3, 4, 5?’ I can yank that part number out of the system and isolate it. I can get analytics, and it will tell me ‘if you take this part out, it is connected to these three product families, it goes through these points within your manufacturing network and is attached to this much revenue.’

And that is a good thing to be able to do because we can always run these low probability, high impact scenarios, especially when it comes to looking at situations where we know we may have to be sole sourced or single sourced. I mean, it happens. And there are some times where you just have one company that makes that one thing you must have.

But at least if you know where that is at in the world and you know what the risks are around that, you can at least put a pin in it and actually start making some decisions on it as opposed to ‘I am not so sure if we are sole sourced, or single sourced, or not.’ And I think if you run an exercise like this, at least for us, it was eye-opening. You find out you are sole sourced and single sourced – maybe one or two steps away from where you do not think you are sole sourced or single sourced.

[Skutnik-Wilkinson] And just think of it in terms of how cool it is then – looking at what the impacts on excipients are. Because it is something that industry struggles with – trying to get people to understand how important excipients are and what you have taken out. Running those what-if scenarios really helps you convey in real situations what that impact is and how that can impact a patient. And I think that is something that we have struggled with in industry for a very long time, and this allows us to help build that story out better.

[Spach] Again, sometimes you cannot do everything in a pre-incident phase. Sometimes you jump straight to an incident occurring, and you have to go straight to the assessment. ‘What data do we have? From this data, what do we need to do? Is there missing data?’ etc. And start building out your playbook from there. But again, our playbooks – the way we built them – are not designed to answer all the questions.



Our playbooks were built as a starting point for where to go. Because when Maria occurred and we didn’t have these playbooks in place, we were in the process of saying, ‘Yeah, we have got to get to those. Let’s get started working on some data stuff first.’ And then we started to get into this environment where we said, ‘wait, we need to start doing something.’

So we built it on the fly as we were moving. And then from that, we came back and said, 'Okay, now let's capture what we did, tweak it little bit, make it a living document, a process within the organization – get buy-in across the whole company for it, and put it into play. And that is what we have done.

And again, it is not a 'what answer fits it all?' It is more of a 'Here is a starting point for what you need to start doing and the steps to start going through.' Because each case can be different. The next one may not be hurricane or earthquake. It might be some other type of disaster.

'Phase in the third step,' is the one thing I always want to tell everybody. Once you start doing some assessment, you have got to find who the decision maker is going to be.

Through the execution phase, you may not impact Janeen's group. You may not impact logistics. You may impact clinical, but you are going to find who is going to be the most impacted line function, typically, and who in that or group is going to be a decision maker, and identify that early on upfront. Because that becomes very critical as you move through this process to be able to make quick, fast decisions.

There would be nothing worse than if we had to sit and spin for a while, waiting for decisions and answers and alignment etc. It was nice to have, 'Hey, we know what is going to be impacted – it is sourcing in our manufacturing sites.' So, we got buy-in from those two on what we needed to do, and they were the decision makers, and then we start moving.

Lastly, how do you transition back to the normal day-to-day operations, once the crisis is over? Maria was a little difficult for us. We technically did not have a crisis. We avoided the crisis, so to speak. But we continued to monitor, and are still monitoring, what our partners are doing and what is inbound for procurement for parts that are still being made here on the island – to just monitor real close what is happening there.

[Skutnik-Wilkinson] Hopefully we have all convinced you, right? There are benefits to collaborations and partnerships, even when you start building something like this. I saw utility in this when we first started talking about it. But even just in the last few weeks, there has been a whole realization of how we can use this for things like our quality risk assessment and some other things that we struggle with when we are trying to help out the FDA and other agencies with regard to what the impact is on excipients.

There is really so much that we can do if we started bringing the right people together, which is something that has been a goal of IPEC since the early days. Collaboration is not just across business functions, but really across industries – bringing the people together from around the world. So hopefully you guys will find this really useful.

[Jones' full presentation begins on p. 18.]



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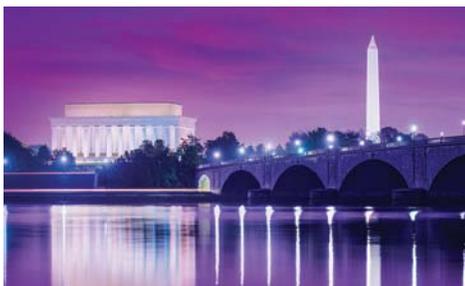
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WCBP 2019: 23rd Symposium on the Interface of Regulatory and Analytical Sciences for Biotechnology Health Products
January 29-31, 2019, The Mayflower Hotel, Washington, DC



CMC Strategy Forum Latin America 2019
12-13 March 2019, ANVISA Auditorium, Brasilia, Brazil



Analytical Technologies Europe: Symposium on the Practical Applications including CE, LC and MS in the Biopharmaceutical Industry
12-15 March 2019, The Croke Park Hotel and Conference Center, Dublin, Ireland



8th International Symposium on Higher Order Structure of Protein Therapeutics
April 8-10, 2019, San Mateo Marriott San Francisco Airport, San Mateo, CA



Bioassays 2019: Scientific Approaches and Regulatory Strategies
May 6-7, 2019, Gaithersburg Marriott Washingtonian Center, Gaithersburg, MD



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Cell & Gene Therapy Products (CGTP): Manufacturing, Quality and Regulatory Considerations
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**CMC Strategy Forum North America
Practical Aspects of ICH Q12 Implementation**
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16th Symposium on the Practical Applications of Mass Spectrometry in the Biotechnology Industry
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CE in the Biotechnology & Pharmaceutical Industries: 21st Symposium on the Practical Applications for the Analysis of Proteins, Nucleotides and Small Molecules
September 29-October 2, 2019, Hyatt Regency Hotel, Bethesda, MD

CMC Strategy Forum Japan 2019
9-10 December 2019, Tokyo Marriott Hotel, Tokyo, Japan

BAXTER'S CHRIS JONES ON EMERGENCY PREPAREDNESS AND LESSONS LEARNED FROM HURRICANE MARIA



At the September 2018 PDA/FDA conference held in Washington, DC, Baxter Operations Strategy and External Contract Manufacturing VP Chris Jones addressed advance and emergency preparedness in the face of natural disasters and other extreme events to ensure manufacturing and supply chain continuity and avoid potential shortages and disruptions. Formatting changes and other minor edits have been made by IPQ for clarity and readability. The normal disclaimer that the presentation represents the views of the speaker and not necessarily that of his/her organization is not included.

My approach to our discussion today is to touch certainly on our experiences with hurricanes, but I am going to spend a little bit more time talking about disaster preparedness and response in general, hopefully sharing some nuggets that you can bring back to your organizations from some of our hard-learned lessons.

When we think about disaster recovery and disaster preparedness, obviously we have got hurricanes. We have Hurricane Maria, and Hurricane Florence just came by. But there are other global events and things that can impact your supply chain that we all should be preparing for to ensure continuity of supply to our patients and to our customers.

Political events: Right now, for anybody who has a facility in Costa Rica, I am sure they are aware that there is a strike that has been going on and off for the last week or so. That is threatening our ability to bring in raw materials and ship product out.

Economic events: If you are watching the news, you know that there is a little bit of an issue with a trade war with China right now. There is discussion of renegotiation of NAFTA. There are a number of economic events that may not create an immediate disruption to your supply chain but that certainly are going to change the dynamic of your business that you are going to have to respond to and accommodate.

Then there are the ones that are **self-imposed:** • quality issues • equipment failures and • things that one might argue are within your control, but that nonetheless have the significant possibility and capability to disrupt your supply chain.

So when we think about disaster preparedness, we think about all these things that could pose a challenge to your business and to your ability to fulfil to your patients.

The Process

The process that we follow at Baxter is really simple. It does not get much more simple than this. But as they say, the devil is in the details. But at its most basic level, it is about monitoring, preparing and responding.

- **Monitoring** is about maintaining a situational awareness – understanding what is going on in the world events and keeping your head up.
- **Preparing** is about building the muscle strength to respond to these crises through training, as well as development of appropriate standard work that you can deploy in the event of a crisis – so that you spend less time thinking about what you should be doing and more actually moving directly into execution, so that you can respond in the most expeditious fashion possible.

- And then **responding**: The coordination of resources is key to ensure that you are deploying resources in the most efficient manner. When there is a crisis, it is human nature that everybody wants to help and everybody wants to chip in. But solid command control and coordination of those resources is crucial so that you can have the most impact and make recovery in the best fashion possible.

And as we are all here, we are all part of the healthcare industry. Really, the goal of all this is to maintain a consistent supply of product to those people who need our products.

Situational Awareness

Digging in a little bit deeper, let's look at situational awareness. There are a number of services out there that you can sign up for that will send you alerts of things of all manner, from hurricanes to earthquakes to changes in company ownership, changes in CEOs. And it is wise to actually employ some of those services and make sure that you have vetted information coming into your company.

Also, we continue to monitor traditional and social media sources for events around the world. The problem is that it is similar to what we saw for a lot of areas today, which is information overload. You sign up for these services, and you almost get numb to them. So what we have done that you might want to entertain doing is we have set up a **threat management system**. So we have situational awareness. We have all the data coming in. And categorizing that data based on risk is an efficient way to apply the right amount of resource.

So we have risk coming in. And at Baxter, we break those risks down into green, orange or red. If it is green, there is no evident threat to our supply chain or our patients – so put that to the side and check the box that we do not think that is going to impact us. If something is orange, it means that it has the potential to impact us. So we have assigned a person to maintain it, to keep an eye on it. And they will have at least weekly reviews on how that threat is progressing.

Red is obviously a category where it is all hands on deck. We have multiple calls daily, and we have a central coordinator who is working through and coordinating all the response activities for a given event. So having a system by which you can manage that data, manage those threats, is crucial in being able to not be overwhelmed.

Training

From a training perspective, it is like any athlete. Repetition is key. So what we have implemented is that every other month we do **scenarios**, where five to seven scenarios are created. In those scenarios, we have fictitious disasters, whether it be civil unrest, a disruption in sea traffic in the Gulf, or some other incident that our plants and our functions have to respond to.

We have about five or seven scenarios. We send them out to assigned owners, usually a plant manager or function lead. And they have seven days to respond. In seven days, they need to come back and tell us what they would do in the short-term, medium-term and long-term to negate the impact, and what potential preventive actions they should have taken to mitigate the impacts of whatever their scenario or the crisis was.

On that seventh day, we pull all the plant managers across the business, as well as the functional leads, to go through their report out. And they basically present their output and then we go through a dialogue of opportunities for improvement. 'Did you think of this?' 'Did you think of that?' And then those scenarios are updated. And we upload them to a shared repository. So it serves as a reference for the future.

Unfortunately, we have had at least two incidents where we had a crisis that we actually had predicted. Thankfully, the plant manager went out to the resource, pulled it down, and was able to execute the plan accordingly. So training is key for preparation for these events, and building that muscle strength.

Then in talking with several individuals who are in quality and from operations, nothing is better than a standard of work. So creating that **standard of work**, the emergency playbook, is critical to our response function as well.

Central Response Coordination

That central response coordination is crucial, both for flow of information in and out. One of the things that happened with Hurricane Maria and subsequent crises is that everybody needs information to communicate out either to regulators or to Wall Street or the press. So having a **central command control center** is critical to managing any crisis.

So we set up a command center, or as we call it, a situation room. It is in addition to those command centers or situation rooms that I am sure that all of the companies have where they focus more on the physical and the human threats and security. This is more about supply continuity, and it augments that room.

So if you have one of those, you might want to think about how to extend it to ensure and protect **supply chain** continuity as well. But having that central command and control of the resources and information is critical to an efficient response.

Lessons Learned from Maria

While I am very proud of the response Baxter had to Hurricane Maria, there certainly were lessons learned for us all. In particular, our facilities were not that badly damaged. We had nominal damage. We had some water ingress. We had some issues to work through.

But what was more of a challenge for us was the **infrastructure**, the roads, getting to and from the plant. Power generation was a learning. We had, as I think most companies on an island had, power generators. The lesson we learned was having a plan for being on our own power for an extended period of time.

We had generators sufficient to run our facilities. But we were not anticipating having to run those generators 24/7 for three months. The storm hit on September 20th, and we did not receive 'stable' power at our [Hianuda] facility until December 20th, a full three months later. That was not really what we planned for. So we are accommodating our plans, which is a big lesson learned for us there.

We heard about the availability of cash. Certainly if you have facilities in remote areas, I would encourage you to consider prepositioning of assets such as cash. Because when you lose power, there are no ATMs and no credit cards, and depending on how fast that storm changes or that event occurs, if it is an earthquake you will have very little notification, you have little time in the midst of that, the preparation for crisis, to position that kind of asset.

So make sure that you are thinking about **proactively positioning resources** so that people can conduct business. And it is not only for the people trying to get groceries or gasoline. It is also for your facilities. You need food for your cafeteria. You need to get fuel to run your generators. You would like to believe in, and in many cases we did have, relationships with our suppliers, where we did not have to worry about that. But there are instances where cash, in fact, is king. So contemplate positioning those resources further.

Cross-registrations: This is about managing expectations. So we have a global network at Baxter. And when the storm hit, we collaborated with the FDA to expedite some approvals, some other sites within our global network sites to serve the market. But it was not able to fully replace all the supply that was coming out of our facility in Puerto Rico. So managing expectations in having a process to communicate is something crucial that we are going to do better in the next event.

In terms of your **supply chain**, again, we felt great. Our facility was intact. Oops, the roads are not cleared. We cannot get the infrastructure to get product in and out. That got cleared and we all felt good. Then uh-oh, our suppliers. Our suppliers maybe did not have as much resources, or support, at their disposal. We had to spend quite a bit of time with the raw materials suppliers, our labs, to really successfully execute our recovery.

So do not forget about your suppliers. You definitely have to look outside your house to the whole value stream.

Government Collaboration

One thing about crises is they normally bring out the best in people and organizations. Hurricane Maria was no exception. There was a tremendous amount of collaboration across the municipalities, the Federal government, and I will speak more on that next.

But reach out to your peers when there is an incident. Do not be afraid, do not be shy. A lesson learned for us – actually, it is in our playbook now, but not before – is if you are not going to do it before, quickly reach out to others that are in the same position as you, so that you can respond appropriately.

People are our most important asset. So really ensuring that your people are taken care of, so that they start to rebuild their lives, is important. These people have lost everything or most everything. They are searching for a sense of normalcy. Help them through the process in any way you can is my message to you.

From a collaboration perspective, within 48 hours, Commissioner Gottlieb was reaching out to our CEO to check in, see how things were going, see what help we needed. They were a tremendous partner through the process, looking for ways to help us.

I personally had three quick check-ins, as did some of the people on the Baxter team, with senior-level folks at the FDA. Just check-ins, wellness checks, how are things going. And maintaining that active communication was critical to staying connected and to quickly raising up any issues that we might have needed help to address.

Key Issues

One of those key issues was expeditious approvals of **alternate supplies**, which again did not fully supplant or replace the capacity we had in Puerto Rico. But it did serve to alleviate some of the pressure.

On more of a tactical level – more block and tackle, as you will – **DHS** [the Department of Homeland Security] was also very supportive and helpful, whatever they were helping us to identify, such as where to house our people. A hurricane hits, several hotels are not functioning. Those that are functioning maybe often were being occupied by federal agency employees or municipal employees who were there to help everyone, not just one company or one industry.

So working with DHS: They were very helpful in identifying where we were going to house our folks. Where we were having some concerns about getting diesel for our generators, they were able to point us in the right direction of who to talk to. Partnering with the federal government and federal agencies was extremely critical to successfully recovering from this event.

But it did not stop there. The **local** municipalities, the local mayors, the interaction with the community and collaboration at that level was equally critical – working together. It is a two-way street. We were getting help from municipalities to clear roads. In turn, we were helping them when we had supplies or could help fix their generators. So having that mentality, that culture, of collaborating between organizations public and private to get through the crisis is crucial. And it was very effective.

A Community Perspective

From a community perspective, we had a number of outreach items. I am not going to go through them all, but there are a couple that I would like to highlight.

The picture in the upper left corner [of the slide] is people lining up for water. On the island of Puerto Rico, I should have mentioned, we have three manufacturing plants, one distribution center, and a commercial center. Two of those manufacturing plants make solution, they make water. So we were able to provide water to the community. And it was heart-warming to see that people were coming to us and we could provide that and we could help people with that.

I never knew the value of ice. You mentioned it, and it seems to be quite ubiquitous. It is something that I learned about the whole experience: that ice is king, right after cash, in these crises.

Helping Employees

For our employees, I could not be more proud of Baxter's response here in what we did, both at a central level and a local level. At a global level, we have established a **disaster relief fund** for our employees. It is employee-funded, and people who have been impacted not only by this particular event but other natural disasters can apply for relief.

It is funded by our employees, but the administration costs are borne by the company. So it is something that is ongoing, it is evergreen, and it will continue to support, as I am sure there will be another situation in the future where people will need help.

We also extended interest-free loans. This really speaks to helping people get back on their feet using whatever resources you have at your disposal to bring that most important asset back to a position where they can come back to work and can rebuild their lives, whether that is providing laundry services or generators or meals. All those things are key to bringing your facility and community back up and running.

Personal Connections

This is basically the distillation of our preparedness now. As I mentioned, I am very proud of our response. But there are plenty of lessons learned. And what we try to do is to take those lessons learned and incorporate them into procedures. This is a high-level map of some of those procedures.

From a people perspective, **establishing relationships** is key. So encourage your plant managers, your leaders in your localities, whether that be in Puerto Rico, or many of us are from global companies, wherever your locations are, know who is around you. So that in a time of a crisis, you know who to go to. You pick up the phone and it is not, 'Hi, I am Chris Jones, it is good to meet you,' but instead it is, 'Hey, Jane, it is Chris again. We talked a couple of months back. Maybe we can collaborate on something here to help out and get everybody back on the running.'

It is always easier to have those conversations beforehand. So we encourage all of our plant managers, all of our leaders, to understand who is in leadership positions in the municipality, but also what other companies are around. So when the crisis waters peak, make friends with Coca-Cola and Pepsi. Batteries are important. If there is a Duracell plant nearby, get to know them! So that you can leverage that relationship instead of introducing yourself in the middle of a crisis when everybody is trying to manage the situation.

Standard Supply Lists

The other thing to do in advance that I recommend is create standard supply lists. I am embarrassed to say on our conference calls I was asking, 'What do you need? What can I get you? What can we bring to you?' The answers are pretty self-evident: baby formula, diapers, water, food, batteries, flashlights – those things. You can think about those things in advance, so we have.

So now we have standard supply lists, where I am not going to have to ask those questions next time. We can be in a position of actually pre-positioning that material in locations such as Puerto Rico, where we pre-positioned said materials.

Employee Policies and Preparedness

The other thing with regards to people that was challenging for us: We did not have enough policies in place in terms of how to manage the situation. I do not mean kind of the supplies, but some of the people aspects of it. Not only do we need to get them supplies, but how do you manage cash? How do we disburse it, because we have a limited amount? How do you decide who gets what? Who distributes it? How do you authorize or sign off or get a receipt for who gets it? All those are things you should not be figuring out in the middle of a crisis. So we have established some policies that prepare for the next go around.

Similar to that, how do you pay people? If people cannot come to work, because both access roads to their home are destroyed, do you continue to pay that person? Having a policy in place so that you do not have to try to make those decisions during a crisis is quite helpful.

And then employee preparedness: Providing employees training with how to prepare themselves, their homes in order to weather such a storm in a crisis is critical. Also how to communicate – whether it be through AM radios or other means.

We actually have issued AM radios to all of our folks in hurricane zones of the Atlantic. Ensuring that they are able to communicate and weather the storm is critical as well.

Site and Materials

From a site perspective, we did really well in terms of our site protection. We had orderly shutdown processes, procedures to protect the plant, despite the fact that our plant was nominally damaged. But we really did not have good procedures on what to do relative to a holistic business perspective before and after the event.

We put together a workshop, and we created a T Minus Seven to a T Plus Five **checklist**. One **checklist** per day – so that when you see a storm coming, or any predictable event. It applies to others as well. T Minus is not so effective for volcanoes or earthquakes. But it works for those that you can predict.

For each day there is a list of activities. We know what the plant should be doing. They know what they should be doing. Again, not trying to figure out at that moment, 'what should I be doing in preparation?' So the T Minus Seven, the T Plus Five checklists have been very helpful. In full transparency, I will admit that we are continuing to refine these as we look at the number of near misses that we have had with hurricanes this year. We are refining those checklists. But it is about continuous improvement and how we can better prepare for the next go around.

Standard Protocol Templates

Standard protocol templates: I mentioned information flow earlier. Every crisis happens, and everybody wants to know what is going on. You call the plant, you finally get that satellite link. Satellite phones, for anybody who has not used one, are not the most reliable phones that you have ever used. So when you finally get hold of somebody, and you ask the plant manager, 'Hey, how is it going,' you probably want a more structured conversation than that.

So we have established standard protocols in terms of what we want to know. When we first make contact, we want to know these five things. And then if there is time to chat after that, then we will chat after that. But because what we experienced was intermittent communications, even with satellite phones, we want to make sure that we are really tight on that information flow.

Relative to **connectivity**, I think everyone on the island has at least three ways to connect to the plant – whether it be through fibre links, whether it be microwave, whether it be satellite dishes. I think we have all learned that hard lesson, where we are going to have redundancy in our communications so that we can maintain communications to our sites.

Another thing that is a little bit of a twist on that is when we brought up our operations, we started to have some problems with access, because of data communications, accessing servers that were needed to process data and store some of our lab data. It was slowing us down. We have actually implemented local data servers for some of those items so that we do not have that delay in our process.

Thinking about cloud **computing**, thinking about centralization of data – that is something you want to be careful of. Be mindful of what system is going to be the slowest, or what system is going to deter you from continuing to operate should you have a breakdown in your communications.

Power generation is another issue. We did not have co-gen at any of our sites. I know we had generators. But I did mention that we lost power a couple of times at our sites because those generators are not designed to run 24/7 for three months. So what we have implemented is an **N Plus One strategy**. Co-gen is expensive to implement. It takes a long time. Well, we did not have enough time from hurricane season 2017 to 2018 to implement a co-gen. What we implemented was an N Plus One strategy. N is the number of generators you need to run your plant. Add one.

So bring one down, do the maintenance on it, do your repairs if it is a breakdown, and you can still run your facility. An N Plus One generator scheme was something that we have implemented. And from a diesel supply kind of issue, the number of times during the crisis where I was crossing my fingers hoping our supplier was going to deliver.... Make sure ahead of the crisis that you have relationships – again, with those local diesel providers that can assure you that they are able to deliver fuel, that you are on their lists, and that they will do their best to deliver. Having multiples is always a good idea.

Maintenance Windows

From a perspective of serving our patients, we talk about alternate registrations. We talked about supplier continuity plans. I would like to touch on: consider very likely your **maintenance windows**.

So our maintenance windows, as I am sure many of yours are, are in December and in July. Hurricane season is June to the end of November. When you go to a maintenance window, you expect not to have some interruptions, so you are going to bleed off some inventory. You get a sawtooth in your inventory levels.

Well, if your shutdown is in July, and prime hurricane season is in September, you are in a precarious position relative to your inventory levels. So what we are doing is shifting our maintenance windows. First of all, we are doing smaller but more frequent maintenance windows. But any major maintenance windows – we are skewing them so that they do not occur so that low levels of inventory are incurring in the middle of hurricane season.

If you do that, if you subscribe to the old school December/July, you may want to think about making it a little bit more skewed, especially if there is any type of predictable disruptions, like monsoons or hurricanes or other that you would want to consider.

Material Movement and Manual Transaction Procedures

Then **material movement**: We ended up having a little bit more inventory on the island than we would have liked, after Irma. We got very little time between Irma and Maria to extract all the materials. So we have now got a finished goods policy as part of our T Minus Checklist. Make sure you are expediting all finished goods out of the area. To that end, we have actually reserved excess capacity we can call on to get inventory off the island, should we need to do so, in a very short order.

Then lastly, **manual transaction procedures**. This was really going against people’s grain. ‘I want to make sure you can run on paper.’ ‘I want to make sure that you can process.’ We have done so much work to make everything neat and everything automated, but sometimes those systems fail.

So now we have procedures in our T Minus and T Plus checklists, where we actually do data dumps of our systems so that we can understand where everything is at, and we can communicate back and forth and can take appropriate actions in order to maintain operations.



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PART II

FDA Rises to the Emergency Response Challenge

With the impact of Hurricane Maria on Puerto Rico still very much in evidence, another area of focus at ExcipientFest in May was how the mission of the FDA is affected and how the agency prioritizes and addresses its core activities when confronted with emergency conditions created by manmade and natural disasters like the hurricane.

At the opening session, FDA Office of Emergency Operations Director Andrei Nabakowski provided an instructive primer on the agency's emergency response capabilities and what they look like in action.

Citing case studies provided by the devastating 2017 hurricane season – with a special focus on the impact of Hurricane Maria on Puerto Rico – Nabakowski reviewed:

- the federal government's emergency response infrastructure
- FDA's organizational structure for handling emergencies, and
- the agency's actual response activities in natural disasters.

Utilizing a series of charts, maps, and photographs, he was able to make sense of the federal government's complex web of agencies, lines of authority, communication networks, and partnerships with other public and private entities. He emphasized the role of collaboration in a vast "partner coordination network" outlined in the 2016 edition of the "National Response Framework" – a guide to how the nation responds to disasters and emergencies.

In providing a sense of scale, Nabakowski explained that the FDA, housed within the Department of Health and Human Services (HHS), "regulates about 20 cents of every dollar that is spent annually by US consumers."

Located within the labyrinthine structure of the FDA, his office of emergency operations (OEO) is tasked with responding to and providing interagency coordination for:

- adverse events
- some foodborne illnesses
- injuries
- product tampering, and
- manmade and natural disasters.

FDA Faces the Daunting Challenges of the 2017 Hurricane Season

After providing background on this extensive organizational framework, Nabakowski illustrated how the entire infrastructure sprang into play during the 2017 hurricane season, and how it coped with multiple and compound problems such as widespread power outages, impassable roads, fuel shortages, and nonfunctioning communication systems.

Key to successful operations under these conditions, he noted, was maintaining focus on a hierarchy of priorities, including:

- safety of personnel
- status of FDA facilities and sites
- assessments of FDA-regulated firms
- impact on availability of products, and
- communications with stakeholders.

The emergency operations director concluded his talk with an appeal to the audience: "Your concerns and challenges, your products – those are concerns to me in my agency as well. The more we can work together on these, the better we as a nation – and the world – will be for the essential products we deliver globally."

[Nabakowski's full presentation is included on p. 26-38.]



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ANDREI NABAKOWSKI ON FDA'S EMERGENCY OPERATIONS AND THE 2017 HURRICANE SEASON

At the ExcipientFest conference in Puerto Rico in May, FDA Office of Emergency Operations Director Andrei Nabakowski provided an overview of the FDA and federal government's emergency operations and the response to the 2017 hurricane season in particular. Formatting and minor edits have been made for clarity by IPQ. The normal disclaimer that the presentation represents the views of the speaker and not necessarily that of his/her organization is not included.

Well thank you, Priscilla [Zawislak, IPEC chair and moderator], for that great introduction. Also, thank you for the great notes you made up on some of the initiatives and ongoing work with FDA [see [IPQ August 29, 2018](#)].

In many ways, that kind of sets a great tone for the presentation that I am delivering here on that collaboration, on that partnership – the interconnectedness of government agencies, of the private sector, and many other organizations – and not just on a day-to-day basis dealing with pharmaceuticals and public health issues, but especially so in the case of emergency response issues.

I particularly want to note how great it is that I can give this presentation here in Puerto Rico – what with the significance and great response from the US government and private sector. So many different groups and agencies worked last fall and continue to work now to address the impacts of the 2017 hurricane, and it is better I am able to provide this kind of presentation here. So, thank you for that.

We have a lot of very technical and very regulatory type topics today and tomorrow, which is certainly very appropriate and appreciated within this kind of setting. This presentation is probably a little bit different.... I am speaking very much about the government organizations.

I hope that it is interesting to the group, because it does not start and end with the government by any means. It is that collaboration, which we have touched upon already, that is so important. And I think the more that our partners and the more that other groups that we work with know about what we do and where we are coming from, the better we all are in future responses.

The Challenging 2017 Hurricane Season

So here we go – tropical cyclones in the 2017 hurricane season: Our GIS, our mapping group, put together this slide, pulling together many of the storms from the 2017 hurricane season. Some of the names will jump out at you.

[\[CLICK HERE for all of the slides included in Nabakowski's presentation.\]](#)

Harvey, Maria, and Irma are listed there. I will go into more details on those storms and their impact – but also others, which might not have been in the news quite so much. I, as Emergency Operations Director, was closely monitoring many of these – including Katia there, which we were a little worried about, and wondered whether it was going to come north at one point, but luckily it did not.

But really, the 2017 hurricane season was just remarkable – devastating. It was the most active hurricane season we have had in over ten years. Notably, it was the first time since we have been keeping records that two category 4 hurricanes impacted the continental United States within the same season.

It has been 85 years since Puerto Rico had seen a category 4 storm make landfall.

Hurricane Harvey, with its interesting path, where it basically hovered over the Houston area and the Texas Gulf Coast, dropped torrential rain for days and days. In some areas, they recorded over 50 inches of rain due to that one event, which is just catastrophic. That is an incredible amount of rain. And it is not just the 50 inches, but the resulting flooding and flow of that water that led to a great deal of devastation within that area.

So here in a nutshell are some of the topics I will be going over: • I will provide an overview of the overall federal response organizations • I will be describing FEMA's organizational structures and response, then • I will be going over what we do in natural disasters, including a spotlight on the 2017 hurricane season.

The Impact of Maria

My staff was looking for some good pictures that we could put out here to illustrate it. We pulled out a total of six here. Three in the top row are showing some of the damage here within Puerto Rico, and then three on the bottom illustrating some of the US government assets which were used in that response.

At the top left, you see, is a toppled power line that we will be speaking more about in a bit. One of the biggest challenges, of course, were the power outages across the island, which had a very strong impact upon all sectors, both public and private.

Federal Response Overview



In the middle, you can see some of the blue FEMA tarps and some of the roads. You could actually see, flying into San Juan, that many of the houses and buildings still have these tarps, even today.

And on the right, the impact upon transportation – that was greatly affected as well, as you know.

At the bottom is shown the US government – that we as a nation, have lots of different assets: physical, logistical, transport, and many different capabilities we have to try to respond to this. But it is not an easy thing, particularly in a disaster of this magnitude – trying to bring all these resources together in a way that addresses the need.

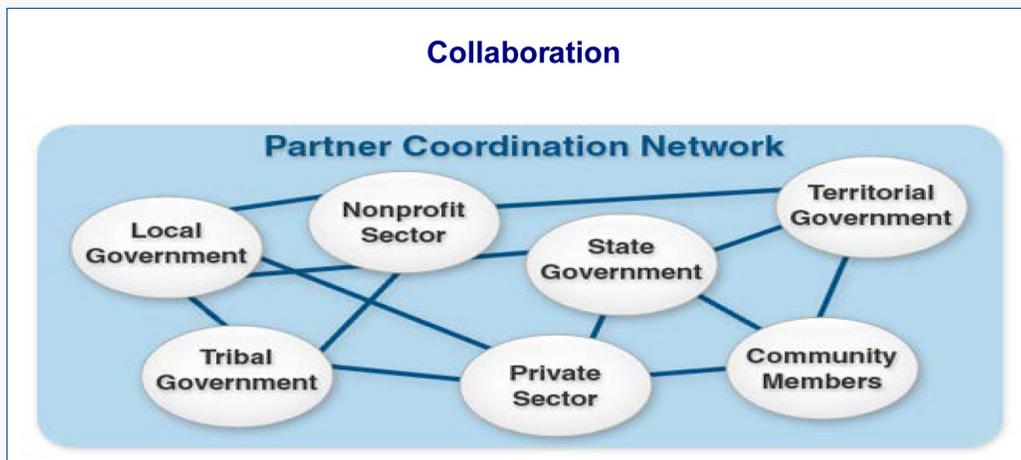
Government Response and Private Sector Collaboration

So, who is in charge? Well, ultimately speaking from the US government side, it starts and stops with the President. The President works directly with the Secretary of the Department of Homeland Security and FEMA, the Federal Emergency Management Agency, which serves as the US governmental lead for coordination of natural disasters. No surprise – I think everybody is aware of that.

But an important point there is, granted, the federal government has structural organizations and assets, but we work very closely with state, local, and private organizations as well. Although sometimes it may seem like it, we do not just unilaterally go in there. We do not invade our states or local authorities.

It is important that we receive a request. Usually it is from a Governor, who will make a request to the US government stating, “Hey, we have a disaster here,” and the President – in a large-scale disaster – will issue a Presidential disaster declaration. That is very key because that is attached to certain regulatory statutes, as well as funding mechanisms to provide US government support to the response. There are also **public health declarations** and other types of declarations as well, which can also pull in public health support and US government support.

Regarding collaboration: As I said, there are so many different players and so many different partners, all of whom are essential. We have the: • local government • non-profit • territorial government • state • tribal community, and • the private sector as well, which is particularly relevant and important to this setting. The private sector has a very important role within the response.



The National Response Framework

How does the government manage this? What kind of guide do we use collectively to try to bring order, to try to bring all these resources to bear? It is spelled out in the National Response Framework [NRF – formally the National Response Plan]. This is the **guide** on how the nation responds to disasters and emergencies.

It is not like a playbook. It is not scripted, like, ‘This unit will do such and such, by such date.’ It is not like that. It is a framework. It basically lays out general, broad-based, responsibilities and roles to enable all these different groups to work closely together.

And believe it or not, I suggest that if you have an interest in emergency management – and we all should have an interest in emergency management – it is worth taking a look at. It is posted in a number of places online. You can go to a few pages and take a look at it. There is a whole section here that deals with the private sector as well, which I will touch on in just a moment. **[A link to the National Response Framework is provided on p. 38.]**

The National Response Framework and the Private Sector

One of the key things that is laid out in the NRF is for the private sector to address the response needs of your employees, your infrastructure, and facilities. We lead with that – and I believe the NRF itself leads with that – because that is very key. Where does it start? Well, it starts with their people – and that is true on the government side as well.

Something important to remember is – particularly here, in the most recent storms that we dealt with – that it was not just facilities. It is not just products and stuff that are impacted. It is people that were being impacted – people and families. And these are our staff. These are co-workers, whether they are working in a pharmaceutical firm or in the FDA space.

As most of you know, we have a district office here in San Juan. I think we have resident posts in other parts of the island. These are our own staff members who, usually on a day-to-day non-emergency basis, we are relying on to go out and conduct normal investigations, inspections, and other regulatory work that we as an agency do.

Well, in an emergency, unfortunately, even though we want to push people out there, even though we want to get it going quickly, our own staff is dealing with their own lack of power and dealing with not having access to water in many cases. They are dealing with transportation issues. And if our folks are dealing with that personally with their families, that is going to impact the ability of our agency to do the things we need to do – and certainly the private sector as well.

I am sure many folks in here ran into those situations where it was disruptive. If people cannot get to your plant, or people are having problems – possibly keeping clean water for the families – then these other things need to be addressed, in order for us, collectively, to be able to move forward.

As to other responsibilities for the private sector, it is important to: • protect information and maintain your continuity of business operations – very important • plan, respond, and recover from incidents that impact your infrastructure and your facilities, and • collaborate with emergency management personnel to determine what assistance may be required, and what kind of assistance the federal government may be able to provide.

Organizational Structures to Provide a Unified Coordinated Response

This is a quick little graphic here showing how the federal government stages itself organizationally for a response. I think it is very appropriate because they put the Joint Field Office (JFO) at the top. Often people look at it rather as cascading down from the President through multiple levels. But realistically, when it comes to the response, it needs to be at the local level.

It is one thing to be back in Washington, D.C., and there is pretty much to do there. But our attention and our focus must be upon what is going on locally – listening to those people in the field who have that first-hand view of what is going on, who are closer to the source and to the problems.

Everyone who is managing the incident there at that level is providing that kind of support. Everyone needs to keep that in mind. It is a very important point.

The US government system has joint field offices, which are run by FEMA. Has anyone ever been to the joint field office here in San Juan by any chance? No one? Ok. They are still engaged now. It is basically the local place here in Puerto Rico where they stage federal assets, where a lot of the collaboration planning for what they are going to do locally takes place.

The next level above that is the Regional Response Coordination Center, the RRCC. Based in the US Government, for the most part, it splits up the country into 10 different regions. On a day-to-day basis, these regions are working on preparedness issues, with local health groups, with local hospital groups, and other partners on a regional basis.

When a disaster occurs, they become the point right above the JFO where they are trying to funnel resources – working with locals to identify what is needed and what kind of resources we can send.

Then, at the higher national level, is the National Response Coordination Center (NRCC) – that is at FEMA headquarters. That is where the very utmost highest levels of the US governmental responses take place.

I mentioned regions. The US government includes the Department of Health and Human Services. For the most part, they have split the country up into 10 different regions – just for administrative purposes – but they are also used during a response.

Now something I will call attention to, and I wish I could have a good explanation of the history, but you will notice that Puerto Rico...is actually part of region 2. And this is pretty much uniform across most parts of the government.

I have asked around every now and then, 'Gee, what is the history of that?' But I have not really gotten a definitive answer. I would like to know one day. Nonetheless, Puerto Rico and the US Virgin Islands are actually a part of region 2 for both FEMA and for Department of Health and Human Services.

Emergency Support Functions

There is the Joint Field Office, which I mentioned. It may not be impressive to look at: a bunch of tables, a bunch of computers, a bunch of folks doing stuff. But it is very key for the local response, because within this facility the US government brings to bear all the different organizations to meet different needs.

They are split up organizationally or functionally. And the assigned leads to each of those needs [come from] different parts of the federal government – to try to come together and provide a unified coordinated response.

Number one there, top left, is transportation – clearly an issue with the impact here in Puerto Rico. The Department of Transportation is the lead. I will not read through all of them. They are all right here. They cover most of the things you can imagine. Logistics, number seven, is a very key one in any kind of response.

And then on the top row on the right side, is ESF 8 – Public Health and Medical Services – the one near and dear to my heart. I have been working for them for quite a while. The lead for ESF 8 is the Department of Health and Human Services.

Emergency Public Health and Medical Services

So, ESF 8: What does ESF 8 do? This kind of outlines, per the US government, what The Department of Health and Human Services [HHS] and its support agency will do:

- public health and medical needs assessments
- health surveillance, solid epidemiology – and CDC obviously plays a very large part in that
- medical care – personnel, supplies and equipment

As many of you know, in natural disasters, the US government has a lot of teams, which we will send out often to augment hospitals. Sometimes they set up medical care at medical care shelters. Has anybody heard of the DMAT - Disaster Medical Assistance Team? Its agency has a number of intermittent employees. They are regular doctors and nurses who are working day jobs elsewhere.

When a disaster is declared requiring some medical support and assistance, these intermittent people are called into federal service and are sent out as teams to provide medical care, often to shelters. Sometimes if there is like a local clinic that is functional, they will set up medical operations there to provide care and support to local groups.

The Public Health Service is a big partner as well. The Rapid Deployment Force is another medical team still going out and providing that kind of care. So that is a big part of HHS' responsibility as well.

- Patient evacuation

You are likely aware that we still have folks who were moved out of Puerto Rico and the US Virgin Islands – a lot of dialysis patients. You may be aware that because of the infrastructure and power impact, they really needed to be moved somewhere else where they could be provided the care that they needed. And we did so. We readily moved them elsewhere. A lot of them up to Atlanta, and some are still there.

- Patient care

I already mentioned, but the next three are all close to the FDA mission:

- Safety and security of human drugs, biologicals, medical devices, and veterinary drugs – a very FDA-like item
- Blood and blood products
- Food safety and security

Other things within the ESF 8 are:

- Agricultural safety and unit security, USDA

Because the FDA is sometimes close to overlapping with food response and safety responsibilities, we do a piece of that as well.

- Worker health and safety
- Vector control

CDC often does a lot of that with DOD, and lots of other things, as well.

Federal Support Agencies

These are some of our support agencies. We do not do it alone. In HHS there is a lot we do have, but there is a lot we do not have. We do not have the most inherent transport capability. We do not have airplanes. We work very closely with some of our other government partners on these kinds of needs.

This is the **Secretary's Operation Center**. This is here in Washington, D.C, in The Hubert Humphrey Building downtown. I used to be deputy director of that about 10 years ago, during hurricane Katrina – my timing with these kind of job selections has been perfect! [ironic] But that was a great job. I really liked that job despite the challenges – maybe because of the challenges.

I know some folks who go home and think, 'Well, what did I do today? What did I accomplish?' Fortunately, I am lucky to be in a field where I know exactly what I was able to do. I find it very personally rewarding.

But nonetheless, here is a picture taken during some of the early stages of the response. You will see in the bottom left in the front row, there in the white shirt and a tie – that is Dr. Price, the previous HHS Secretary.

There is Dr. Alex Azar, whom many of you may know. He has significant experience or background in the private sector, as well. He was also the deputy secretary back when I was in the operation center. He was deputy secretary through Katrina as well. It is really good to see him back now with the significant experience that he brings. We have also Dr. Adams there, in the bowtie. He is the current US Surgeon General. And then of course on the right there, we have Dr. Gottlieb, the FDA commissioner.

This is an organization chart of the **Department of Human Services** – lots of different groups, I think pretty much everybody is going to be involved in a disaster. A few of them are highlighted here.

Those in blue: We have the FDA, CDC, and the NIH. In red: You will notice on the left, that is the Office of the Assistant Secretary for Preparedness and Response.

Now, as I mentioned before, when it comes to the overall governmental coordination, DHS and FEMA are the leads to coordinate across the US government for the overall response. We have a similar mechanism with the Department of Health and Human Services to coordinate across all of these groups – to work with FDA, to work with the CDC, and to work with all of these different groups across the whole department. And that is the ASPR [Assistant Secretary for Preparedness and Response].

FDA Regions, Field Locations and Offices

Has anybody been to the FDA in White Oak? I will try to shed a light on what we do.

We protect public health by ensuring the safety, effectiveness, and security of human and animal drugs, biological products, medical devices, foods, cosmetics, and we also regulate tobacco products – a more recent addition to our mission.

And you have seen the various numbers quoted. But roughly, the FDA regulates about 20 cents of every dollar that is spent annually by US consumers. I have seen it as high as 25 cents. But we will go with 20 cents for this presentation – a significant piece of the gross domestic product.

This is the most current FDA organizational chart I could find with the major offices, dated in March of this year. You can look that up on our webpage. The purpose of me showing this is to show that just as HHS has many different groups within the department who may be involved in a response. FDA itself does as well.

On the bottom here you see most of the major operatives – CDER, the Center for Drug Evaluation and Research, CFSAN [Center for Food Safety and Nutrition], food safety folks. Pretty much all the major centers are on the bottom, but then of course there are many other groups that will be responding as well.

Being the government, you cannot do anything without lawyers. It is true for the private sector as well. We have OCC [Office of the Chief Counsel] involved. We have an Office of Human Rights. And we also have the building facilities folks in the Office of Operations.

Now I will confess, on a day-to-day basis, typically I do not work very closely with the facilities people. They do their job. They do it well. There is never really an issue. We do just fine.

But it is not quite the same when we have a major disaster which is impacting not only the nation, but our own facilities and stuff out in our district offices. Our facilities people become very important. You do not really appreciate them until you realize, 'Gee, there is no power. How much fuel do we have for those generators down there, and what kind of resupply do we have going?' They become very important indeed.

But anyway, there is the over all, and then here is my simplified one. It is probably not technically FDA approved, but I think it shows a little clearer some of the major groups when it comes to the product centers and the different areas that we are responsible for.

So, once again we have: • CFSAN – food safety • Veterinary Products • Medical Devices • Biologics • Drugs • Center for Tobacco, and • Office of Regulatory Affairs. ORA has direct oversight of all of our district offices and resident posts – mostly investigators, inspectors, and those who are going out to visit facilities. Most of them are ORA staff, though occasionally we send out technical experts from the centers, and sometimes they will accompany them. • Then we have the Office of International Permits as well.

Just as earlier I described how the ASPR, the Assistant Secretary for Preparedness and Response, works across the entire department at HHS, my office, the Office of Emergency Operations, plays a similar role within the FDA, working across all these different groups – all these many little offices and groups here – to try to provide a coherent and unified agency response.

There are many different players, particularly in disasters of the magnitude we saw last season, which was cutting across everything – whether it was food, whether it was medical devices, whether it was drugs. Every product sector was involved. We had to pull in expertise and information from across the entire agency, and ours is the office that does that.

FDA Field Locations and Regions

I want to show you a few other organizational charts as well. An important note here: This is the previous chart showing our field locations in the regions. Just out of pure curiosity, how many folks have heard about **FDA program alignment?** It is fairly new. We actually just got to the one-year point since it was implemented.

I will not spend a lot of time on it, but in short, we went from a previous arrangement of our few locations with the district offices and resident posts throughout the country, including Puerto Rico. We used to have 5 different regions that we operated in. Everything was pretty much geographically-based when it came to the field and field inspections.

But about a year ago the agency – ORA saw the greatest impact – shifted to a different arrangement. While it is still geographically-based and we still have folks out there, instead of having a chain of command from the investigator through the local district director, geographically based, and then back up to the headquarters, they realigned it so there is a very strong and close linkage between the different program areas.

I will show you a few of those charts to try to explain it a bit better.

Coordination Between FDA Offices

This is the **Office of Biological Products Operations** (OBPO) in CBER. Before, you would have investigators in each department in our different district offices, and in different resident posts and such, all geographically based. That is how ORA and the agency looked at it. Now, it is being looked at as two different divisions for biologic products. We have Division 1 and Division 2.

Today, the Program Director for Biologic Products Division 1 has responsibility and some oversight over all biologic inspections taking place within that entire division, which runs across many states and many FDA district offices as well. Same with our counterpart in Division 2, which is this massive swath of the Western US.

I will show you a few others as well, because the important point here – you will see this in a moment – is that we have differing numbers of divisions based upon what the program area might be.

This is part of the **Office of Pharmaceutical Quality Operations** (OPQO) – drugs and CDER – probably very relevant to this group here.

There are four different divisions there. And you will see that we do not have an overlap here. We have a number of divisions with different areas being covered by the different product divisions. So that is drugs.

This is **Medical Devices**. It has three different divisions, and you will see it in the little chart there on the bottom. We have tried to link which geographic district offices are tied to which of the divisions to make it easier.

And this is **Food**: Food is not just numbered by a program division. It is split off into east and west as well. It gets very complicated. The little table down there goes into further detail about that.

Then there is the **Office of Enforcement and Import Operations**. There used to just be one Import division. That was the Southwest Import District, which some of you folks might have been familiar with. Now we have expanded. We have different divisions for the entire country.

Hopefully some of it makes sense, but I wanted to focus and zero in and give you an example of one geographical district office and try to make sense of what the impact of this might be – like here in San Juan, since we are here and it is most relevant. The **San Juan district office**, once again back in the day, did all the inspections for that geographic area under their control.

The district office still exists. But now, depending on the nature of the products or sector being engaged with, we will have different program divisions associated with it.

For Biologics it is Division 1. For Drugs it is Division 2. Then for OBIMO [Office of Bioresearch Monitoring Operations], we have Division 1, which is not the same division as biologics. So, it falls in multiple different product divisions.

Needless to say, from my perspective, it complicated things. Before, we would just go to the geographic district – go to their district director, go to their emergency coordinator who was in that district – and it was very clear who we needed to reach out to.

Well, it is still clear. Rest assured, we still reach out to the same emergency coordinators we did before, because that is still geographically based. There is still a lead district director for each of the geographic areas. So that is still true, and throughout the hurricane, that was pretty much what my office defaulted to. We went to the same emergency coordinator.

However, during the response, we had to pull in these different program divisions depending on what the commodity interest was, which made it a little complicated at times.

Office of Emergency Operations

My office is the Office of Emergency Operations. We are the ones who work across the agency, pulling in different groups, depending on what the nature of the response might be. The National Consumer Complaint coordinators are actually within our office. Folks may know that in each of the district offices are consumer complaint coordinators who are working for ORA, but the National Consumer Complaint coordinators are actually within our office.

We work with complaints of product tampering. We will work with the local district in the OCI [Office of Criminal Investigations] on that. Significant reports of adverse events and illnesses that may be product associated, we are usually involved in those as well – working with the centers to come up with a speedy resolution or to identify what exactly is going on and what regulatory steps may be needed.

Also, we work interagency on a day-to-day basis. We work with lots of other governmental groups on emergency planning and response plans.

As a matter of fact, there is a national level exercise that just kicked off this week, and rolls into next week as well, which my folks back in the office are dealing with right now. It is a two-year planning cycle for this particular national level exercise. And as luck would have it, the scenario they came up with about two years ago was a hurricane. Needless to say, we got some thoughtful input to bring into this exercise. My office is one of the very few groups within an agency that actually acts with true 24/7 availability.

But if there is some type of emergency where something happens, whether it is a weekend, whether it is a holiday, whenever – middle of the night – the agency needs to be reached. Whether it is by one of our fellow partners or a consumer with a truly concerning issue which needs to be dealt with, or industry as well, we actually have staff who will take that call and work, regardless of the hour, to get it where it needs to be and do what needs to be done.

This is our **operations center**. This picture was taken during the hurricane, probably, based on the staff there, since we had to rotate people throughout the country. I would say it is probably late September, early October. This is not just my office. As a matter of fact, most of the people you see in there actually are not from the Office of Emergency Operations, although we have a nice little cluster up in the left there.

But this is where we bring together our partners to work at the headquarters level during a response. We have representation from all the different sectors in there. From this facility, we were able to bring together subject matter experts to come up with what we as an agency needed to do – to prepare reports that we needed to send back up the chain for the commissioner and to the department.

Also, we stood up a **Joint Information Center**, which was able to respond to public inquiries.

The name of the organizational group that we put together for this response is the **Incident Management Group**, or IMG. Essentially, it is a coordinating group which is not stood up on a day-to-day basis. We only pull this group together as needed to deal with major emergencies. It is a fairly uncommon thing, which is probably a good thing for my staff and the hours of work, but we pull it together certainly for these hurricanes. We pulled it together for Hurricane Sandy.... There have been a few foodborne illness outbreaks for which we have also pulled IMG together.

The IMG reports back to the Commissioner and the Commissioner's agency executive group. This serves as the agency's highest, senior-most level, which typically deals with policy and very broad regulatory agencies.

If we run into something where we have a problem, and it may or may not exactly be addressed in the regulations, we need to do something. We need to make sure that our senior-most leadership is weighed-in to determine the direction the agency will go. So, this is where the commissioner and his level weigh in on the response.

On a day-to-day basis, the IMG itself is led by the Agency Incident Coordinator [AIC]. It is the AIC that sets the mission and takes care of day-to-day operations and planning, then reports back to the commissioner. For all but one week of the 2017 hurricane response season, I was the AIC.

This is the **Incident Command System**. Is anybody at all familiar with ICS when it comes to emergency response? It is a very standardized and set organizational structure which is used across the entire government – a lot of military groups are adopting it as well – which sets rules and responsibilities of an organization during a response. It is very useful.

Actually, it grew out of a fire in our national forest system, back in the 60's. They had some very hard lessons learned, unfortunately, about how to manage staff and resources during wildfires. There were some tragedies, and they realized other organizational approaches they might take. And because of their expertise and how well it worked, it was gradually adopted by the rest of the US government.

That is an actual organization chart showing the IMG structure broken down. On the left we have operations – an Operation Section Chief who reports to the agencies and coordinator. You have a Planning Section Chief, also reporting to the AIC. It is not just planning, but they are also very key when it comes to information management and documentation. Along with the emergency itself that we are dealing with, sometimes it is like you are in a whirlwind of emails and phone calls and everything else, and trying to make sense – trying to set what we call a ‘**common operating picture.**’ A COP within an emergency is very, very important.

While the rest of us are being dragged from a phone call to a conference all throughout the day, you need a group of staff who are dedicated to first reading, and then analyzing and assessing incoming information to try to help out key decision makers determine where we are doing well, and where we are maybe not doing so well, and where we need to change our tactics.

Then of course logistics: very key – moving stuff and getting stuff to the facilities. I referred earlier to the field stuff, very key – then of course, admin and finance as well, because nothing runs without dollars.

Overall Agency Response

I know it might not be too impressive looking, but what you have here is the AEG, **Agency Executive Group** – the Commissioner at the top – that means the management group who has the overall agency response. This actually has a date on it. This is interesting enough to include. This is from September 22nd, so this is after we had the Harvey impact, and Maria as well.

We had incident management teams stood up at each of the district offices who were engaged. Notable here is Dallas, Texas, working on Harvey issues. That is the green. We also had New Orleans, which you guys probably know is immediately adjacent to the Dallas district. There was also some coverage impact there. There is a little green triangle there.

The light blue – that is all Hurricane Irma. So, you have San Juan. You had a little bit of Irma impact there. Florida district, which was greatly impacted by Irma – it funnelled right up the state to the Atlanta district and then to New Orleans, as well. We had Baltimore on standby for a while out there, because we were still uncertain how the storm would track. Also, we wanted to have them on to assist the Florida district.

We had Philadelphia and New Jersey districts on alert to either provide additional assistance if needed, or to find out what the track of the hurricane might be.

Looking back, every now and then I will have people ask – because we waited until August 28, close to Harvey’s impact, which activated the IMG – ‘Well, do you think you should have stood it up right on landfall?’ Now, retrospectively, we made the right decision to do it then. Because initially, it takes a while to assess how much impact there is going to be and what kind of resources will be needed.

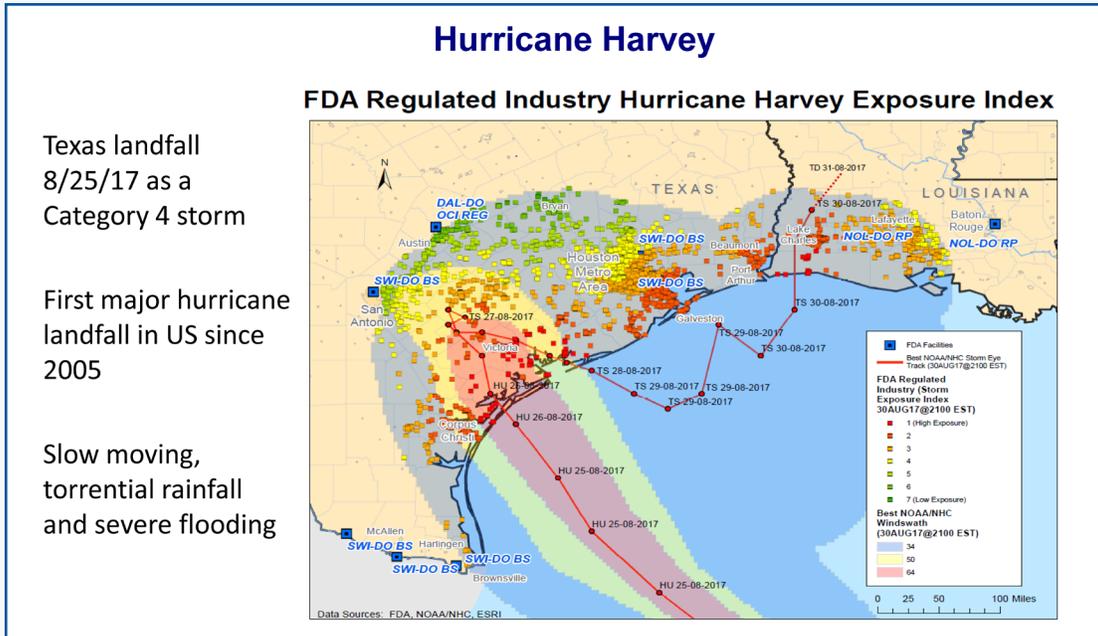
Then for the most part, the FDA – we are not first responder types where you send people out to do swift water rescues and stuff. We are not doing that. We do not send our people into dangerous situations early on in response. So overall, we are pleased with that timing.

Hurricane Strength Information		
• Tropical Storm	39-73 mph	
• Category 1	74-95 mph	Very dangerous winds, some damage
• Category 2	96-110 mph	Extremely dangerous, extensive damage
• Category 3	111-129 mph	Devastating damage
• Category 4	130-156 mph	Catastrophic damage
• Category 5	>156 mph	Catastrophic damage

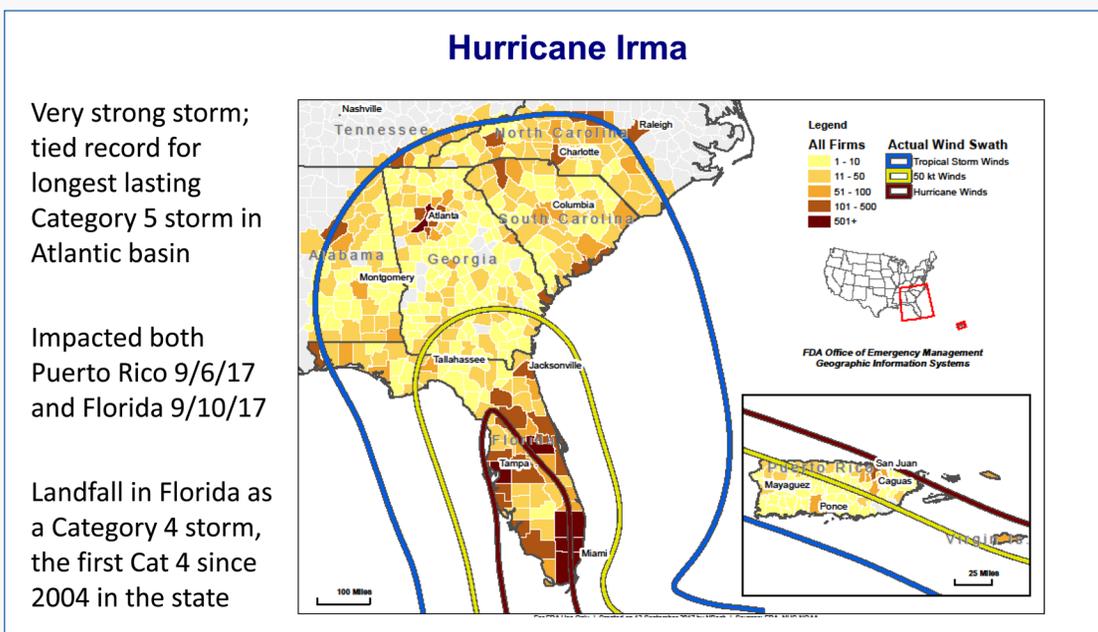
The 2017 Hurricane Season and Other Challenges

I am going to provide an overview of the wind strengths, and kind of a relative scale of the damage. A Category I hurricane kicks in at about 74 miles an hour, which are some very dangerous winds and cause some damage. But that 'some damage' is probably deceptive, because when Hurricane Sandy hit landfall, it actually made landfall as a Category I, and we all know how damaging that storm was. And it gets increasingly worse with higher damage as you go on up to Category IV and Category V.

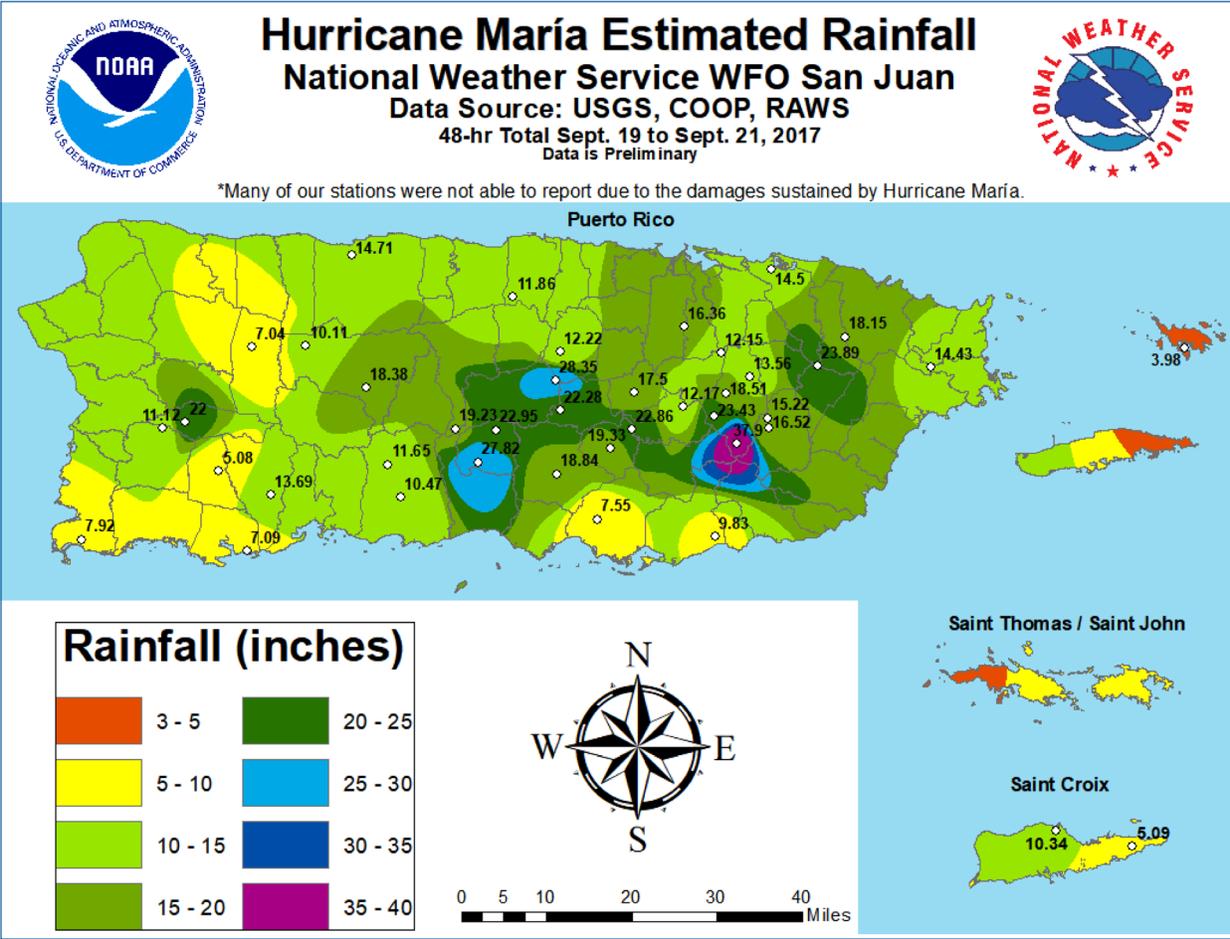
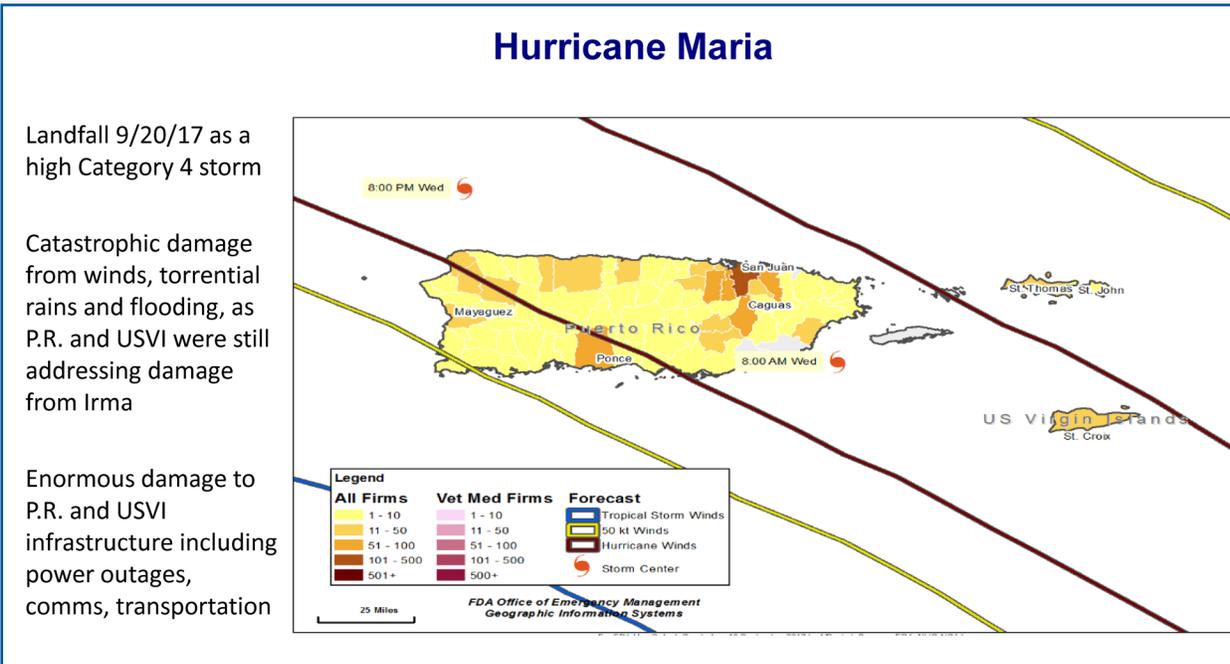
Hurricane Harvey made landfall August 25th as a Category IV. I already mentioned the significant, damaging – incredibly damaging – rainfall that we had there, which we had to address.



Hurricane Irma came up through Florida, as I mentioned, and had skirted Puerto Rico. We were kind of fortunate it passed a little bit to the Northeast, but it still had some impact.



Then of course, there was Hurricane Maria, which struck as a category IV with devastating effect upon Puerto Rico – and with huge amounts of rainfall. We put this slide up here because we thought the downed power lines best illustrated some of the things that we face.



Challenges we faced included: • widespread and sustained power outages • communications down all over • roads and transportation greatly affected • generators – I mean, did your sites have generators? We know ours did, but not everybody's did. If they did, did they have fuel? And did they have maintenance in place to last them through the extent of outages? • damage across all FDA regulated product areas, and • the duration of the response itself. The IMG was active for months, not only at headquarters level, but our people here in the field are still working on it.

This is a photo of our district office here in San Juan. It is not as devastating or as startling as some of the other damage photos that are out there, but you can see there is damage to the structure itself. Our lab was down, and it had significant impact on the facility as well.

Our areas of focus included: • personnel accountability. Number one is our people – people first, and we take it seriously • status of FDA facilities and sites • the assessments of FDA regulated firms • impact on products availability, and • communications with stakeholders.

I mentioned the **Joint Information Center** briefly as well. This was the first time that we, as an agency, have stood up and formalized a JIC this way. It is very useful in dealing with public inquiries and putting together a unified agency message. It was very useful. One of the examples of their product is here. **[A link to the FDA Office of Emergency Management is provided on p. 39.]**

Other Challenges

In the midst of our response, we also had to deal as an agency with other disasters and ongoing activities elsewhere, including wildfires in California. This was very significant in itself, because once again, it crossed almost all of our product areas.

Here we were, dealing with all these storms. We cannot just ignore it. We have to deal with it. We as an agency ran into some challenges with that. Instead of pulling the IMG, we kept the IMG dedicated to the hurricane response, and split off a separate group to work and be dedicated to the wildfire issues as well. And it was a challenge for some of the other groups, because the same expertise, the same experts that were aligned with the hurricane, were now being pulled into other directions. But it is something we needed to do and something we did do – very successfully.

Okay, my final slide is 2018 hurricane names. Today is May 1. Does anybody know when the hurricane season starts? June 1. One month from today the 2018 hurricane season is kicking off. So, we have more of this ahead and the challenging question I pose to you is: Are you ready – based on your knowledge, your experience, and everything you did during this last hurricane season, and based on the lessons you have learned for your own sites and facilities? I hope that it has been taken to heart. I would love to hear from you individually.

I would love to hear some of your personal experiences, some of the personal challenges you and your organizations have dealt with, because we have that in common. Your concerns and challenges, your products – those are concerns to me in my agency as well. The more we can work together on these, the better we as a nation – and the world – will be for the essential products we deliver globally.

[[CLICK HERE](#) for all of the slides included in Nabakowski's presentation.]

LINKS:

- [The National Response Framework](#)
- [FDA Office of Emergency Management](#)



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- Understand rapid drug development pathways
- Define and understand risks and mitigation of those risks
- Interpret the latest regulations and requirement of Data Integrity
- Establish relevant control strategies through streamlining of parameter classification

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AGENDA

PART III

Natural, Societal, and Political Drivers Are Putting Supply Chains at Risk

Also addressing the ExcipientFest conference, author and Risk Cooperative CEO Dante Disparte provided a global view of the natural, societal, and political drivers that are putting supply chains at risk.

Disparte began his talk with an overview of three “mega-trends” and their impact on the pharmaceutical industry: increasing natural disasters, troubling trends in human population and urbanization, and the impacts from human activities that result in climate disruption, social unrest, and political upheaval.

Disparte’s colorful talk was grounded in real-life experiences, ranging from the feared failure of the Oroville Dam in California to a ransomware attack that infected computers in 150 countries within three days in 2017. He emphasized that most companies and communities are unprepared for this kind of eventuality, and asked, “Where in your industry do you have...the ‘fire brigades’ we are increasingly relying on to respond to these complex threats?”

Focusing on intellectual property, which he noted is so essential in the pharmaceutical industry, Disparte observed that “there is a back door for everything these days,” and that the best way to withstand the potential impact of cyber threats is to be transparent, because “organizations that are proving to be inconsistent with their stated value systems when these revelations occur, have the biggest price to pay, compared to organizations that are consistent.”

Investing in Resilience is Cheaper than Paying for Recovery

Perhaps the key point Disparte made was that investing in resilience is far more cost-effective than paying for recovery after a disaster. He cited Puerto Rico’s unhappy situation following Hurricane Maria, noting that a \$20 billion investment in infrastructure resilience prior to the hurricane

could have offset a projected cost of more than \$94 billion to rebuild after the fact.

Disparte concluded his talk with an admonition that society needs to invest now in bio-defense to prevent or mitigate against the spread of vector-borne diseases like Zika and Ebola, which could traumatize the developed world just as they are impacting the developing world.

During a question and answer period following his presentation, Disparte noted that there are four big issues that “keep him up at night:” • climate change • severe income inequality • cyber risk, and • the erosion of global trust. “Those four things are real problems right now and you see them on our streets, you see them the headlines, you see them in ballot boxes all over the world.”

He also honed in on another question that he is deeply concerned about: “The morning after Brexit the number one Google search in London was ‘What is Brexit?’ and second one was ‘What is the EU?’ – raising some really profound questions of what does it mean to be a citizen of a western democracy?”

He further noted that according to the World Bank’s rating system of ease of doing business in different countries around the world, Puerto Rico rates 52nd and is declining. He then asked rhetorically: “How then do you argue for consistent long range capital from the private sector when there are so many other places in the world where you could put that money with potentially less complex labor laws, with fewer strikes and riots in the streets, and with the better guarantee that the infrastructure will work?”

In his final comment Disparte pointed to the USA’s broken tax code as motivating corporations like Apple to hoard billions in cash outside the US instead of investing here. “That is not really great for the country, and all of us are going to end up paying for that,” he concluded.

[Disparte’s full remarks are included on pp. 40-51.]







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RISK COOPERATIVE'S DANTE DISPARTE ON THE IMPACT OF GLOBAL DISRUPTIONS



At the 2018 Excipientfest conference in Puerto Rico, author and Risk Cooperative CEO Dante Disparte discussed the challenges of preparing for and mitigating the impact of climatic, political and economic disruptions. Answers by Disparte to questions following his presentation are included. Formatting changes and other minor edits have been made by IPQ for clarity and readability.

I am, of course, incredibly grateful to ExcipientFest for this great opportunity to come back to Puerto Rico. It seems fitting that on a day that you invited a risk expert to speak, there is a national strike, with footage that is more akin to countries in South America or perhaps France than part of the United States.

And let us keep that theme in mind because in 2016 when I wrote a book called 'Global Risk Agility,' little did I know that it would almost read a bit like the prophecies of Nostradamus and that in the year after so many other things that we were trying to chronicle with my co-author about the emergence of man-made, natural, and emerging risks – that those three big forces would have massive impact on the world, and that 2017 would in so many ways be the opening act.

I have long argued that what happens in places like Puerto Rico – if you think about the impacts of these hurricanes recently – are the canary in the 'climate change coalmine.' And how the world responds to helping 'build back better' in the Caribbean will say a lot about what happens in the continental United States and what happens around the world.

Here where people are marching – and some of us ought to be in solidarity with them; as goes Puerto Rico, so goes the rest of the world – is sort of setting the stage. I will try to regale you with the fun tale of all these complex risks.

My industry, the risk and insurance industry – and I spend a lot of time as you might imagine in the national security community in DC – is the last line of defence. Yours, the pharmaceutical industry, is the first in the complex world that we live in. And yet both of us have operating models that are all about 'long tail.'

In your world, you put a lot of capital in R&D and you wait for that next blockbuster drug to emerge. In mine, we put a lot of capital at risk, waiting and hoping to dodge the bullets that have visited upon our country, and Puerto Rico specifically, with incredible and terrifying accuracy. We have not dodged too many of these bullets.

So what we will try to describe are some of the macro-level trends, and then drill down. I promise you I am an optimist, but some of what follows is a little grim. Okay, so where are we now?

Increasing Risk of Natural Disasters

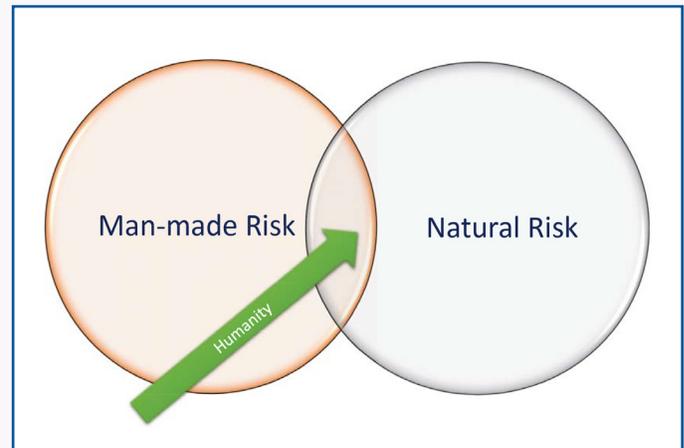
Anthropologists look for what they call a golden spike or a marker that marks the end and the beginning of the new geologic age. So right around 1950, we entered the Anthropocene - it is a big word, but all it means is the age of man.

Not surprisingly of course that also is the atomic era. What these geologic markers look for is when a shift has had big enough impact on the planet to mark the end and beginning of new era. So, that is where we are right now.

Why this is incredibly consequential – and we definitely felt it in Puerto Rico – is that man-made and natural risks are converging.

When you think about our industry, the insurance industry, we have massive solutions – all kinds of very sophisticated products like catastrophe bonds, insurance policies, and the rest – to respond to naturally occurring events. But there is one very big distinction between the two: An earthquake does not plot where it is going to occur.

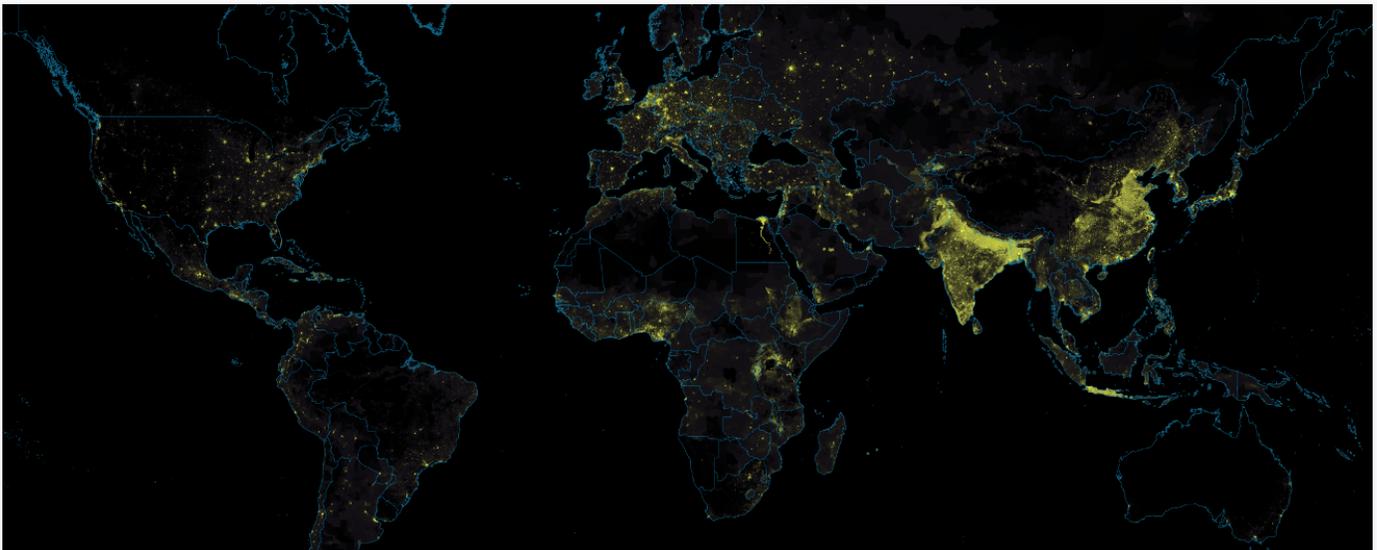
These terrible windstorms that we saw similarly do not plot where they occur. In effect, they are capricious by nature. They are surprise events, and there is not much you can do to prepare for them or stop their course. Man-made risks on the other hand, and we will talk about a few, they have agency. So if you harden your organization on the right, the risk can shift left. It is a smart risk.



As Tom Ridge, Governor Ridge, who was the first Secretary of Homeland Security and one of my colleagues always says, 'In that domain you have to be right 100% of the time. The risk has to be right only once.' And that is enough to sow incalculable hazard on your organization.

Urbanization and Population Trends

So, a quick Q&A because I can see that everybody is eager to get to that cocktail hour. Can anybody tell me what this slide shows? The answer is 'population.' Why does this matter? If one mega-trend is the convergence of man-made and natural risks, the other mega-trend is urbanization – not just population, but urbanization. And this really, really matters to your industry.



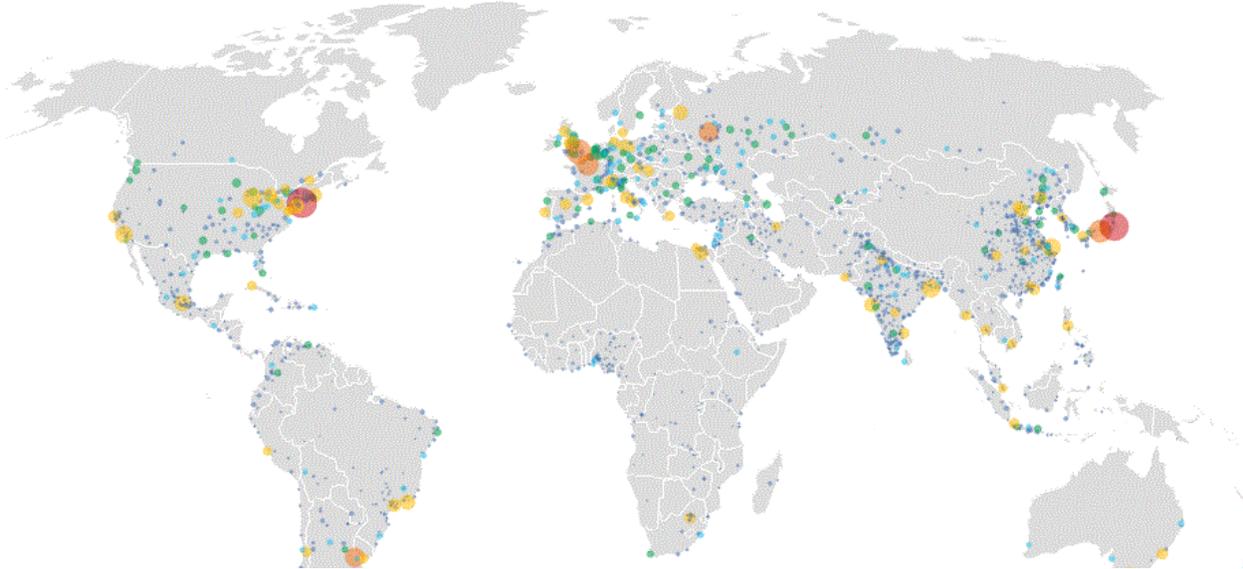
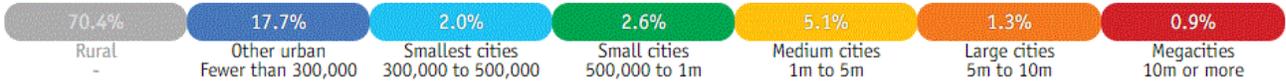
In 1950 those red dots mark megacities – cities with ten million inhabitants or greater. And in 1950, we only had two on the planet - New York and Tokyo had that dubious distinction.

By 1960, you start to see an almost organic aspect in the development of these megacities around the world. But already the world is tilting eastward, and note that those orange dots are not trivial. Those orange dots were cities between five million and ten million, and why does this matter to your industry?

Well, a dense urban environment is an environment where it is very, very difficult to combat the spread of communicable diseases. In effect these cities are at once a place for great opportunity and economic mobility, but they are also festering cauldrons of disease and complexity. Sorry New York, sorry Tokyo, but it is true. As we advance, you start to see more of these megacities popping up south of the Mediterranean and in Latin America.

Urbanization, 1950

GLOBAL CITY POPULATIONS*

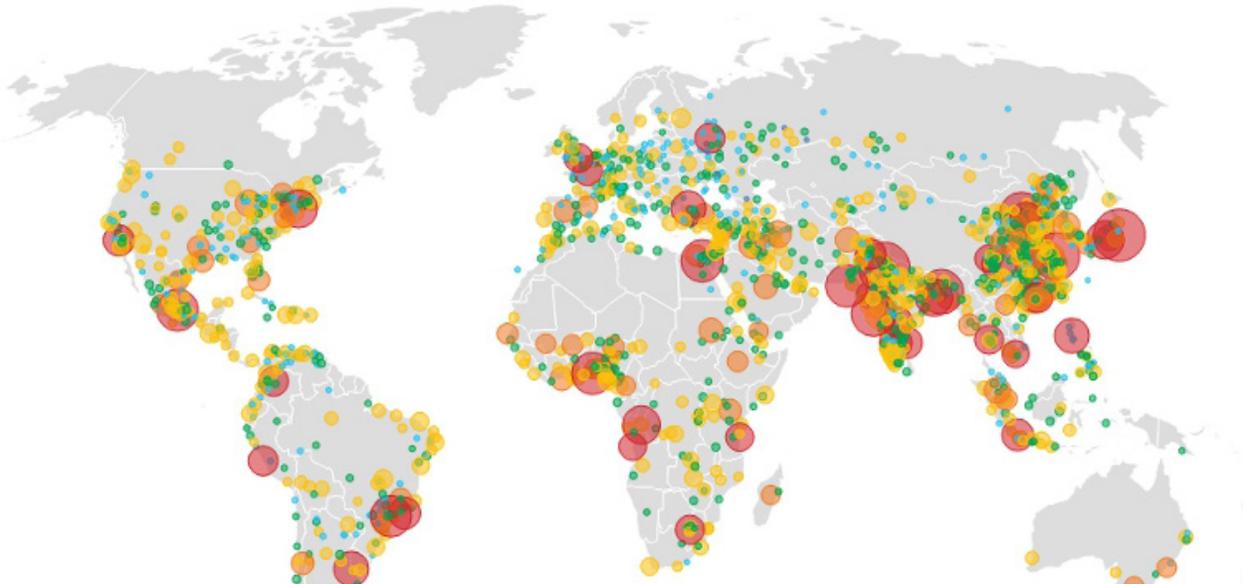


By 1980, Latin America gains two megacities with Mexico City and Sao Paulo, Brazil. In 1990, you see a shift and I think you get the drift of where this is going. By 2030, this is what the world looks like. We will have at least 43 megacities on the planet. Already today 301 cities around the world generate more than half of total economic output on the planet. So you could argue, is this a world of nation states, or is it a world of city-states?

We saw that in the United States. We will talk about some of the political tendencies that we have in the US, but the mayors of many cities in the US and the governors of many states look more like heads of state than they appear to be local leadership.

Urbanization, 2030

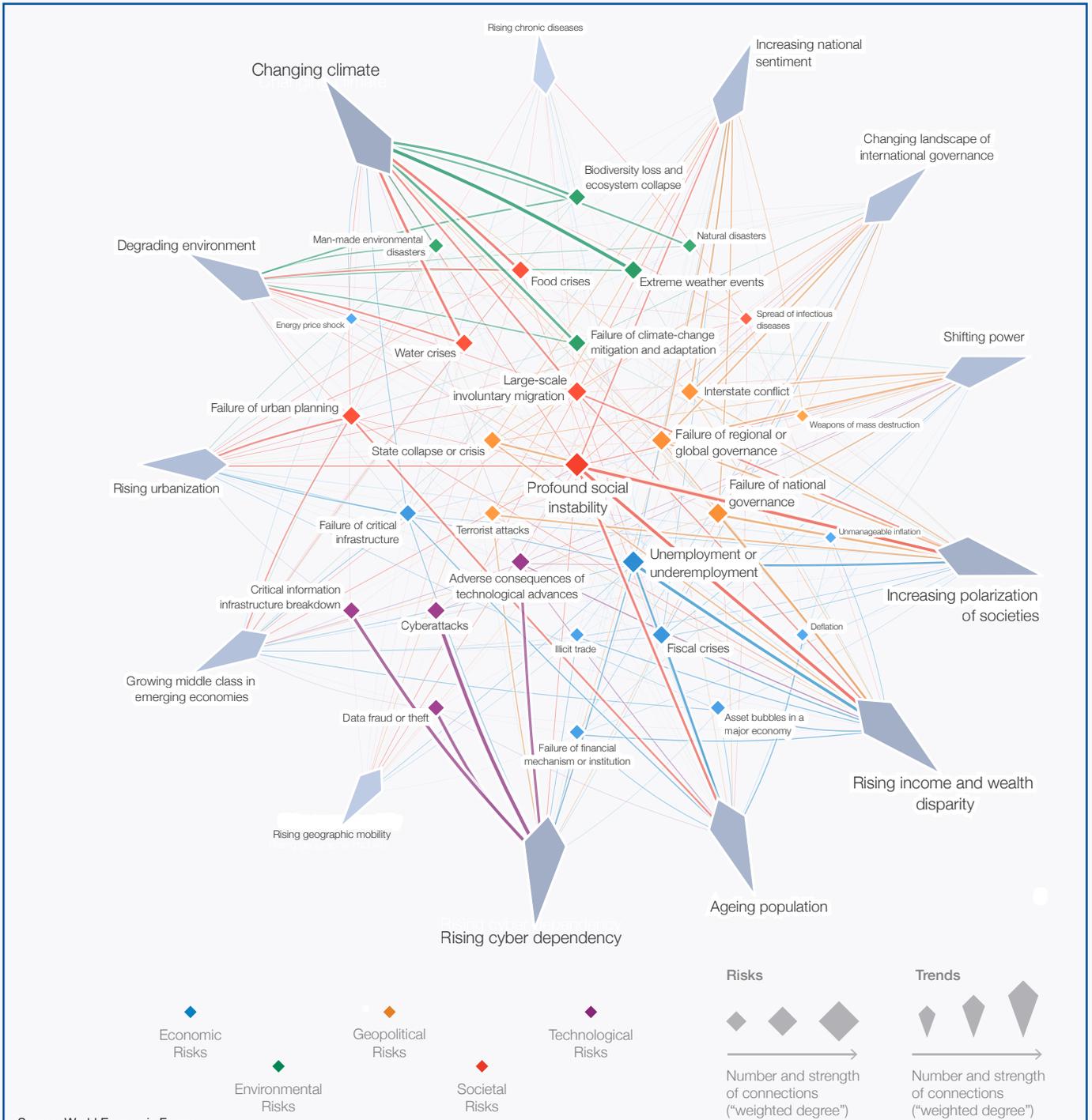
GLOBAL CITY POPULATIONS*



So, when the United States backed out of the Paris climate agreement, New York City said: 'We will abide by those standards.' When some cities were trying to defend their immigrant population, they said: 'We will be a sanctuary city, and if ICE is coming after immigrants in New York or in California or whatever the case may be, we will defend that turf against the federal government.' It is a strange posture, but it is born, in fact, out of this global tendency of urbanization.

So, the map I showed you in the beginning – already today more humanity lives inside that circle than outside. Why that matters to the pharmaceutical industry is because that is a region of the world with a lower level of infrastructural development, healthcare development, and response development. And yet we live in a world that is deeply interconnected. So, that is one mega trend.

Convergence of Man-Made and Natural Risks



Source: World Economic Forum

Mega Trend Three: If the first is a convergence between man-made and natural risks, the second is heavy urbanization, mixed of course with globalization and interconnections. The third is the convergence of all of these complex risks.

In 2015, for the first time in the research on risk that the World Economic Forum puts out each year, all of the major factors around the graph are man-made or man-driven.

Alright, it is a big, big shift from a world where wild fires might occur naturally and serendipitously, to a world where they are going to be fueled by manmade drivers. It becomes increasingly complex. I call this the wheel of misfortune [[see previous page](#)]. So let's give it a spin and see what it looks like.

Let's begin with climate change, which is relating to the experiences that Puerto Rico has endured. The Atlantic hurricane season was the most intense and most persistent and most severe we have recorded. And I always pause on this slide for a minute to let the one degree distinction sink in. So, many in climate circles – and this is the only slide that I promise that looks anything like Al Gore's – he stole my slides for his speeches. But the one degree difference is key.

For a long time the climate science arena has discussed this notion of a two-degree Celsius increase being potentially the ceiling, over the next 30 years or so. What we are now facing is a prospect that the two-degree Celsius mark may very well be a floor and we have to really start thinking about a world that has much more radical and accelerated climate impacts. And in so many ways 2017 was the opening act.



Think about the prospects then if you are in Panama, for example, and your country relies on the Panama Canal as a big portion of its economic drivers. The prospect of a northern open ocean sea route is not far off into the future. Already you have Danish Shipping Companies like Maersk planning to build hulls that can withstand these types of journeys. That basically makes a big part of Panama's economy completely irrelevant.

So in those shifts we have got to ask ourselves a lot of questions. And I think that organizations like yours need to confront who are going to be the winners and losers long range of this type of complexity?

The Atlantic Hurricane Season

We have talked briefly about the Atlantic hurricane season. The real opening act of the Atlantic hurricane season was Hurricane Harvey. Harvey arrived in the Gulf, dropped more rain on Houston and the Gulf states than had ever been reported in US history – effectively collapsing the GDP and the economy of the fourth largest city in the United States and a major choke point for oil. Clearly the supply chain impacts had far reaching implications. Until today, there are many households and communities in Houston that are waiting for insurance money to come in, and waiting to recover.

When you pull back the lens and you think about how the United States then responds post 9-11 and the creation of the department for FEMA and security: FEMA had around a billion dollars in its response budget when Harvey hit Houston. FEMA goes to Congress, gets an eleventh-hour line of credit, allocates money that is earmarked for Harvey. And then Irma shows up and destroys, of course, parts of Puerto Rico, which many forget.

Irma left nearly 900,000 people in Puerto Rico without electricity. So we are nearing the anniversary of an energy matrix that has completely failed the island. And then of course Irma destroys much of the Florida panhandle, creating the largest ordered evacuation in US history. Basically all of Florida had to pack up and leave – pretty extreme. It is hard to argue for Fortress America in a world where these types of forces don't respect, nor check in with Border Control, and Homeland Security, and TSA.

We have got to really rethink what it means to be resilient, and I will get to how it affects pharma in a few minutes.

And then of course on the heels of Irma you have Maria, which spared no one in Puerto Rico. And I will tell you just for two seconds my own hurricane survival story. My sister and I lived in a house not far from here, an ocean front house when Hurricane Hugo hit Puerto Rico in 1989. From that point forward our house was completely devastated. And with that, so was the prospect of a normal upbringing.

Imagine what has happened then with a hurricane the magnitude of Maria hitting an island that was functionally bankrupt, with an electricity grid that didn't work before the storms, and you are just begging for trouble.

The way we organize our societies and our economies has to change if we have any hope of withstanding these shocks. And we do not want people marching and rioting on the streets – not just in Puerto Rico, but in Washington and elsewhere. We really need to revisit what it means to be a resilient society in this type of complex world.

Other Emerging Risks

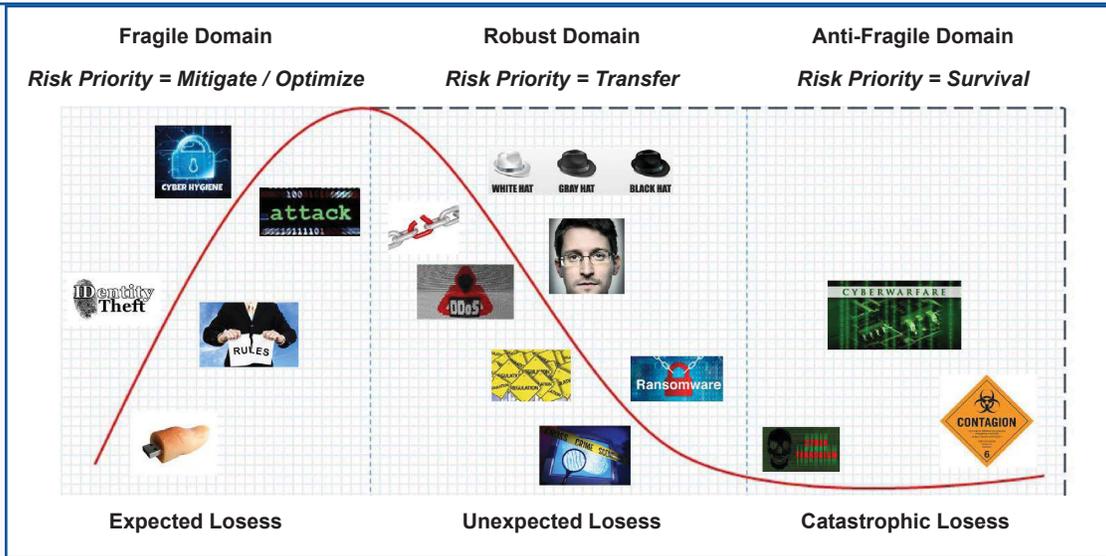
So all of these complexities at the climate change level are not just big, you know 'boil the ocean' problems, they are also very much 'micro-climate' issues. So, this here is a picture of the Oroville Dam in California:



This dam was not engineered for a certain threshold of rainfall. And again from a statistical point of view, if you are building things or manufacturing drugs and pharmaceuticals that are meant to withstand what is considered normal, and then all of a sudden normal skews, the dam fails and causes the ordered evacuation of 300,000 people downstream – how do you then respond if part of what your business model depends on is a normal operating model and normal infrastructure and all of these goods that we rely on in the public space? We all have to get our industry off the sidelines.

So we will spin the wheel of misfortune one more time – and bear in mind, as I said before, that I am really optimistic about a lot of these issues. The reason being is that we cannot respond to things that we cannot measure nor understand. And the fact that many of these effects are starting to harm us and really hit the United States in different ways means that we can now marshal our ingenuity, our people, and our resources to respond.

You hear all the time about our dependency on technology and cyber threats, if you will. What are we going to do about it? Cyber risk, as a general category, is the thing that keeps a lot of people awake at night – whether it is the internal exposures that you see on your left hand side of the screen or something of the internal threat variety. Many would argue that Edward Snowden was more of an insider threat to his organization, the NSA, than he was an actual cyber vulnerability. And in the last domain over here are what are considered catastrophic losses, the losses that are now entering sort of a new normal.



Last year, over the course of the weekend, a ransomware attacked [up to] 150 countries in three days. And each of us made one phone call when that virus hit our computers. We were trying to call our cyber security specialists and technicians. What we realized is that there is a huge shortfall of talent that knows how to respond to these types of events.

Where in your industry do you have the talent gap when you need to get that breakthrough drug across the finish line? And where are those folks that don't view it – whether it is pharma, insurance risk, or cyber security – as a place to put their engineering talent? Where are they? Because those are the fire brigades we are increasingly relying on to respond to these complex threats.

The other piece of course is IP. I think in your world so much of what you build is intellectual property. In this domain of complex cyber threats, it is very hard to assure that any and all of the things that you count as breakthroughs are truly going to be yours and remain in place for very long when there is a back door for everything right now.

The best way to withstand these threats is to be able to withstand sunlight. Organizations that are proving to be inconsistent with their stated value systems when these revelations occur have the biggest price to pay compared to organizations that are consistent. So consistency with your value system will go a long way.

And again the cyber exposures: Because of the way we rely on the world and how the world relies on information and technology, it is not just the complex cyber attacks and ransomware attacks. It is also that we can defend our posture by having pre-invested in resilience.

This is an image of New York City in 2003:



I do not know how many of you were on the East Coast or living in the East Coast in US, but there was a great blackout that plunged the East Coast seaboard and put parts of Canada into darkness for about a week. And there was no deliberate action. The information we have suggests that it was trees touching power lines in Ohio, causing a cascading series of failures.

Indeed Puerto Rico's grid has given out before. I think it was 2013 the entire grid gave out, partly because we were not investing sufficiently in withstanding the shocks of these events.

Investing in Resilience vs. Recovery

We have argued in our work that in this world it is much better to put more capital upfront to pre-invest in resilience than to pay after the fact. Puerto Rico was \$73 billion in debt before these crises and it might have been a \$20 billion investment to shore up the island and its infrastructure and its energy grid. But by waiting as we have, we now have basically 150% of Puerto Rico's GDP that needs to be invested in the Island to get it back on its feet.

PREPA [Puerto Rico Electric Power Authority] is a big contributor to that public debt: that was about \$12 billion of the island's debt. The governor of Puerto Rico, stealing my term "Build Back Better," calls for \$94 billion of investment. In that world, it would have been much, much cheaper and more cost effective to slowly allocate the capital over time, build better systems, and not let the problems of the island fester. So, these crises all come to roost in some terribly insidious ways.

Ask the Gulf states how they feel about losing a big percentage of their population post Katrina. Similar to Puerto Rico, we lose the very facets of the culture that make these types of islands and regions like New Orleans very special when thousands and hundreds of thousands of people are displaced.

One of the founders of Google, Eric Schmidt, talks about this concept that data is the new oil, and a lot of us hear a lot of these terms everywhere we go. But to me the comparison stops there, because oil is a global commodity and an asset that has a valuation – something that we all understand. Having spoken to thousands of organizations about their cyber insurance, what we realized was people are spending billions and billions of dollars trying to protect informational assets. And yet, when you ask them how much protection is enough, not one can give you an answer, and it does not matter how big they are.

So we realize there is a huge gap in this concept of 'valuing enterprise assets and informational assets.' Pharma has a very unique quality to that as well. So much of your asset is R&D, and this has a long, long development process and horizon. But how do you then value that and quantify that, and therefore shield that as one of your more important assets? So that would be a few words on that concept.

Current Societal Problems

Let's spin the wheel twice more and then we will try to land the plane on time and hopefully there will be questions. So the other big mega trend that we are observing right now is all man-made. And when I say man, I really do mean it is the men who are driving these problems.

Right now we are living in a world with very, very deep societal **polarization**. You feel it across the Atlantic with the oldest of the global institutions that we have erected since the Second World War, whether it is NATO, the United Nations, trade agreements like NAFTA – all of these things that were meant to keep the world stable. And our former rules-based economy is being shredded to pieces.

The very concept that the EU, born after the Second World War, was about the free flow of the goods, services and people – try doing that today under the pressure of the migration crisis and under the pressure of the return of economic nationalism and national retrenchment.

This is complex because we are facing challenges that require of the world deeper engagement – not retrenchment. As I said earlier, it is hard to shield against threats that do not recognize borders, and we will see in a moment as we talk about pandemic disease and biodefense issues, we need a much more engaged world than we have right now.

The social polarization is taking place on the streets of San Juan, as the police put up barricades trying to defend people's property, assets, and potential liability risk, and others. But look at Ferguson, Missouri. And Baltimore not long ago, not far from me in Washington, DC, was set alight – in part because the social pressures are not going away.

Often times my business is international, and often times people call me because they are concerned about these types of risks in emerging and developing countries. But for the first time, the phone is ringing with international investors wondering: can we protect them and shield them against these events here in the United States? And the answer is it is harder because the risk is bigger, and after baseball our second biggest pastime is the way we sue each other.

Regional Conflicts, Migration, and Global Trade

And then you think of these really, really scary events like the conflict in Syria that continues to rage on. Everything that was erected after the Second World War was meant to stop this, and yet it has not been stopped. And here you have a war and a conflict by proxy between all of the great powers and all the regional powers.

Now that the North Korean and the South Korean issue begins to de-escalate, if there is anything on the planet that is putting us on a collision course for unintended consequences, the issue in Syria is it. Red lines mean nothing, human suffering means very little, and these cauldrons create a lot of cynicism about the global system.

The migration crisis in Europe was sufficient to strain the integrity of the EU. And again, think about your world of pharma and biodefense combating the potential spread of communicable diseases in the world – where the haves and the have-nots are forced together in dense urban environments, and the interchange of people because of globalization, world trade, travel, and the rest.

It just forces us to think very differently about how do we secure the world and guarantee prosperity? In that world, you see a rise of economic nationalism, the variety of which we just discussed a moment ago. But one of the things that people forget – and I am not sure how it has affected your industry, concerning trade agreements and NAFTA, and things like that – but most of global trade is actually intracompany trade, it is not international trade.

Companies trade with each other. So the Pfizer or the Merck subsidiary in Puerto Rico might buy excipient ingredients from its parent company in Germany to then finish the product here, for example. But a world in which we are putting tariffs on everything and anything – in part because everybody is going to have a tit-for-tat approach to trade wars and the rest – is going to end up creating a higher ultimate cost for the consumer and a higher ultimate cost for the organization, not to mention all the supply chain disruptions and uncertainty that creates.

Investing in Bio-Defence

How does this then affect pharma directly? Quick question – and I know that we have some folks in the room that are with the federal government, so maybe they are excluded from answering this question: How much money do you think the US federal government allocates for bio-defense and pandemic risk in total?...

About \$6 billion. And when you think about how the US federal government – what a sprawling organization it is, and how it is allocating that \$6 billion – you should take no comfort, nor should you sleep terribly well at night, because the \$6 billion is being spent in an incredibly disaggregated way. Part of it is going into NIH. Part of it is going into direct frontline supports, CDC, and the rest. This is borrowing from a blue-ribbon panel chaired by Governor Ridge and Senator Lieberman to look at this question and to propose ways of improving.

Again back to Puerto Rico: Why does this matter? It matters, because little pests like the mosquito do not check in with TSA. They do not respect national borders. One in five people in Puerto Rico was affected by the Zika virus. And without any hurricane damage and without any smoking craters, Puerto Rico's economy was already beginning to suffer an additional whack on the head, courtesy of complex risks.

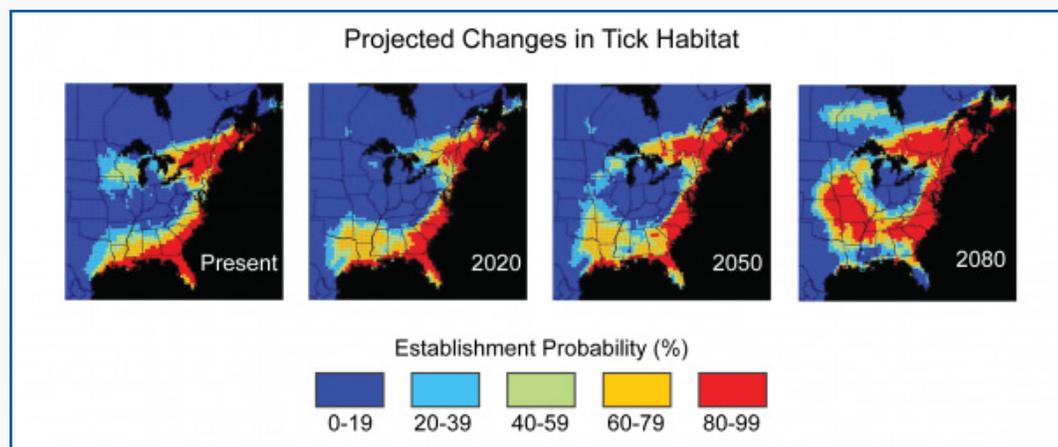
Hotels were facing perfectly sunny days, but there was a big drop in occupancy due to fears. For the first time in US history, the CDC issued a travel advisory against travel inside the continental United States for parts of Florida, particularly singling out pregnant women, but more generally the broad population, as we were uncertain what would be the impact or health effects from Zika.

Is this round one? Is this the first salvo? Hard to say. But how do we then tell the pharmaceutical industry: 'Stop what you are doing. Stop seeking out the cosmetic blockbuster drug and pivot your supply chain and your operation to help respond to an acute global threat? And by the way, we are not going to give you much money.' Good luck telling your shareholder meeting that that is what you have decided to do. How are you going to say that to your stakeholders in your industry? And yet you are the very front first line of defense.

Tom Ridge and I wrote an article for the Harvard Business Review calling for exactly that trade off. Are there instruments that the insurance industry could put together for your trade that will help create some degree of resilience as you pivot your supply chain and your business to respond to these acute emerging issues?

Diseases Without Borders

This is what a heated, densely populated world looks like. Hard to argue for Fortress America. What you see here is the expected spread of vector-borne diseases like Zika, Chikungunya. There are so many exotic names I cannot even rattle them off or pronounce them correctly.



With vector-borne diseases already making their inexorable march north, what do we do? Do we build Fortress America? Let our neighbor's issues fester like we let Puerto Rico's issues fester? Or do we flip the switch and engage? It is complex, but I can assure you, you folks in the pharma business have absolute certainty and professional guarantees that your industry is essential in the future. The rest of us need you to get this stuff right.

And then we look further afield: The Ebola crisis in West Africa was an enormous near miss for the planet. I was in a former company at the time, and we insured a number of people that were affected in the region. Every line of global public health defense failed in West Africa. The local healthcare systems failed. The international NGOs failed. The UN systems failed. And it was not until we militarized the response, which if you think about that – if that is our last line of resort and it had to become our first – how do we then resolve these issues the next go-round?

Changing the Mindset

Confronting the root cause of these issues, investing long range, and really thinking very differently about operating models are how we will thrive among uncertainty. The uncertainties are already here. We do not have to wait for some Hobbesian future. It is here now. But we do have to recalibrate the way we operate and think.

Most of the work that we do really relates to **risk management** and decision-making. I hope there are some takeaways from this type of audience, being in the trade that you are in. When you think about risk management as a practice – and it is maturing as a practice – unfortunately, it has a lot of flaws in it. And therefore I wrote a clever little book that advocated for some ways of substituting those flaws.

The first is that most risk management is backward looking. It presupposes that if you cannot measure it, you cannot manage it. Therefore, you are only looking for what is known as a kind of model error, and you are going to only find data that supports your position and posture.

The other piece is that risk management is largely driven by surprise events. So for the risk manager in an organization or project, their job is avoidance. That is success. It is not proactive. It is not entrepreneurial. It is not really meant to be a decision driver in an organization. And last but not least, risk management is treated as a cost center in most organizations. And I am sure if you have any experience in project management, or finance, or other traditional cost centers like ops, etc., you know what it is like: You are neglected all too often.

I have been advocating that these types of challenges really belong at the senior-most levels in an organization. They have to be forward looking. They have to espouse some degree of entrepreneurialism. Decision avoidance is not a decision, and status quo is not a posture. You create conditions like the ones we have in Puerto Rico when you let things fester and there is only status quo.

We have to do things that are much more proactive with all of this. So the agile risk manager is a person who is ‘values driven’ and can create value by helping the organization spring back.

Long Range Resilience vs. Short Range Profit

Elon Musk is trying to combat climate change by trying to completely make the internal combustion engine obsolete. He is redesigning what it is to think about urban mobility, in part because the world is a heavily dense world, and people who get stuck in traffic for many hours show up and do silly things when they get to work.

How do we then take our core businesses and our business models and totally rethink what it means? Instead of maximizing profit – ‘as much as I can have and as fast as I can have it’ – how do we optimize the assets, the resources, the power so that we can withstand shocking events and we can withstand the types of situations we have here?

All of this requires investment. Everything that I described, if you stretch out the investment horizon long enough, can be smoothed out. All the peaks and valleys can be resolved. But we have to totally rethink the operating model. Pharma, you do this by default in the way you develop and you run R&D. It is very much about long-range work.

But are you only putting your R&D on things where there is a known market? That would be an example of setting yourselves up for failure. Because it may very well be the thing that is of highest need and highest demand was somewhat acute, and not just a cosmetic or where you had a known marketplace, because so many of these markets did not exist many years ago.

You think about the cyber security industry: The whole industry blossomed in the last 5 to 10 years, and multi-billion-dollar companies now exist where there were none before. So every other facet of global resilience – whether it is climate change, human adaptation and bio-defense against pandemic risks – will have multi-billion dollar firms emerge that are in part driven to help us respond and become more resilient to those types of events.

Disparte's Answers to Audience Questions Following Talk

Q: With so many risks out there – you mentioned a lot on climate change, disease – what keeps you up at night most?

What keeps me awake at night is our lack of preparation for pandemic risks and biodefense. One person tries to blow up a plane with their shoes and everybody now takes their shoes off at airports. The Spanish influenza killed nearly 50 million people. That lack of proportionality is scary as heck. And the ease with which our neighbors' suffering doesn't affect us is scary as heck.

So I think we have got to completely shift our focus towards things of that nature: bio and pandemic risks. Spending a lot of time with people like Tom Ridge makes for a lot of fun in these types of conversations. But when you ask people in the national security arena what are they most concerned with, it is that.

I call it the big four: • climate change • severe income inequality • cyber risk, and • the erosion of global trust. Those four things are real problems right now. You see them on our streets, you see them in the headlines, and you see them in ballot boxes all over the world.

The morning after Brexit the number one Google search in London was 'What is Brexit?' and second one was 'What is the EU?' – I am not kidding, I wish I were – raising some really profound questions of what the heck does it mean to be a citizen of a western democracy? And what is the whole model we are fighting for and striving for and our businesses are allocated against, when we are completely turned off by even our neighbors problems? So, I think those would keep me awake at night.

Q: How much of this type of presentation are you doing with the kids in school. Because we are old. We don't care. Some believe in climate change. Some do not believe. I think you should instead of talking to the grass root, talk to the kids.

I couldn't agree with you more. When people realized that democracy was something that mattered and voting mattered and political engagement mattered, we started to show up. And you are right, so many of us – and myself included – are merely going to observe and chronicle what is happening on the planet.

But others are going to be the beneficiaries or the casualties, and I am encouraged by the level of activism we are now seeing. But complaining without a posture is not a strategy either. So yes, my next book will be a coloring book, and I will focus very much at the grass roots level. It is a brilliant idea. And I don't take it facetiously. I agree with you.

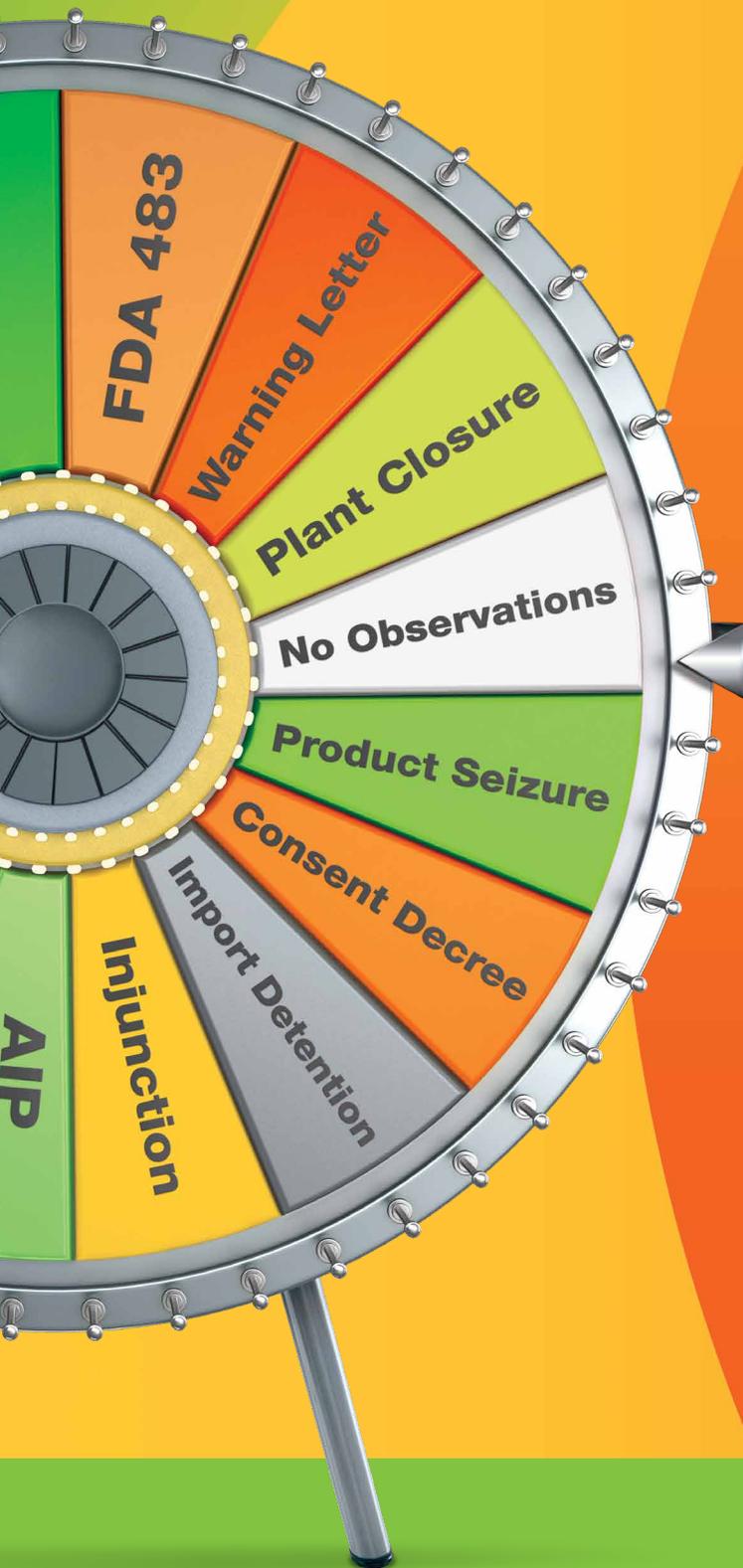
Q: How do we look at risk assessments, for instance, with our crumbling infrastructure for transport? Coming from manufacturers, we still have to get product across the country. And we are facing a crisis with trucks and roads, so is that part of looking at risk assessments for manufacturers?

Absolutely, no question. How do you build a resilient system? All of this is interconnected. A few years ago I helped to bring out this report in DC called 'The US Competitiveness Project.' It is all about the fact that the common elements on which we rely – the infrastructure, our talent pool – all of them are eroding: the US score card on infrastructure, on education...

Think of this metric: The World Bank has a measure of the ease of doing business around the world. United States is around #8. Depending on the year that you asked, Puerto Rico is #52 or in the 70's, even. And, of course, it is continuing to decline.

How then do you argue for consistent long-range capital from the private sector when there are so many other places in the world where you could put that money with potentially less complex labor laws, with fewer strikes and riots in the streets, and with the better guarantee that the infrastructure will work?

All of this requires a completely different thesis. Companies hoarding cash, like Apple – nearly a trillion dollars on its balance sheet – that are not putting money back inside the United States because of double taxation issues – that is not really great for the country, and all of us are going to end up paying for that.



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PART IV

Expert Panel Discusses Impact of Hurricane Maria

After Disparte's presentation, a panel discussion was held that provided an opportunity for the presenters to dialogue further on the challenges and lessons learned in managing Hurricane Maria and other crises.

Moderating the discussion was Pharmaceutical Technology Editorial Director Rita Peters. The participants included Colorcon's Puerto Rico plant manager Victor Amador and Global Regulatory Affairs Director David Schoneker, author/advisor Dante Disparte, Biogen's Lee Spach and FDA's Andrei Nabakowski

The focus of the discussion immediately turned to the human impacts of disasters, with Amador providing an emotional first-hand overview of what it was like dealing with the challenges faced by his staff in the months following Hurricane Maria.

All public services had gone down as a result of the storm, and the unavailability of power, fuel, supplies, water, and food put enormous stresses on company employees – especially those who had lost their homes or who had to care for relatives who had lost their homes.

FDA Takes Exceptional Actions After Maria

Nabakowski explained some of the exceptional actions FDA was able to take in face of the challenges posed by Maria. These included: • expediting approvals for alternative manufacturing sites • facilitating the import of products from overseas to address local shortages, and • allowing extension of expiration dates when a company could provide reasonable assurance that it was safe.

He also noted that the agency made some exceptions regarding specified storage temperatures, and took the unusual step of working with other federal, state and municipal agencies to organize alternative transport by sea and air of critical medicines both into and out of Puerto Rico.

Spach reiterated some of the key points made during his earlier presentation. He emphasized the benefits of geo-mapping the company's suppliers in order to insure against being too dependent on one vulnerable region, and examined the benefits and risks of custom-designed, single-sourced components versus off-the-shelf versions available from multiple sources.

Disparte followed with an analysis of how the costs of recovery after Hurricane Maria were multiplied as a result of the lack of investment in basic infrastructure that had plagued Puerto Rico before the storm. He also cited the lack of insurance coverage in high-risk areas, noting that for every 1% of additional homes and businesses insured against disasters there is a corresponding 22% reduction in tax-payer-funded recovery costs.

Schoneker, who is serving as IPEC-Americas vice-chair for science and regulatory policy, suggested ways of further responding to the crisis, including IPEC members that have facilities in Puerto Rico creating a forum to communicate, share planning, and work together in preparing for and dealing with the impacts of future disasters.

[Some of the key panel interchanges are provided on pp. 53-57.]

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PANEL DISCUSSION ON THE IMPACT OF HURRICANE MARIA

The following is a part of the panel discussion that took place at ExcientFest on the impact of Hurricane Maria on Puerto Rico and the people working in the pharma-related companies there. The discussion was moderated by Pharmaceutical Technology Editorial Director Rita Peters. Participating in this part of the discussion were Colorcon plant manager Victor Amador and Colorcon Global Regulatory Affairs Director Dave Schoneker, along with author and Risk Cooperative CEO Dante Disparte.

Peters: I am Rita Peters, currently Editorial Director of Pharmaceutical Technology, but earlier in my career I was an editor for a business continuity publication, so this all seems to become a full circle right now.

Just to point out here some of the other natural disasters that happened really just in last half of 2017 – but also to point out that, besides those that make headlines, there are many business interruptions and disruptions that can happen on a much smaller basis.

Back to the **impact on Puerto Rico:** Damage estimates of \$90 billion. Estimated fatalities both direct and indirect of more than a thousand. Obviously the media followed the news about power, communication, utility issues, and more than 60,000 buildings lost there. While flying in yesterday that was still quite obvious.

The impact on the pharmaceutical industry here – these are FDA numbers: In 2016, 30% of Puerto Rico's GDP was composed of pharmaceuticals and medical devices that were manufactured on the island – obviously, a large economic impact there. And 11 of the top 20 global pharma companies have a presence here, so the impact on those individual companies is also significant.

But we are here to talk about supply chain and the impact on patients. About 8% of pharmaceutical expenditures by Americans are for products manufactured in Puerto Rico. Puerto Rico produces more pharmaceuticals for the US than any foreign country, and also more than any state.

So, again, big impact. We already had concerns in the industry, and now there are quite a few drug shortages. FDA identified potential shortages of 30 drug products and 10 biological devices or biologics as a result of the storm.

So today our panelists are going to talk about the storm. We are going to talk about the aftermath and some recovery. We are also going to talk about some proactive measures to maintain the viability of the supply chain, and we are also going to talk about some bigger picture items.

Our first panelist is Victor Amador, who is the plant manager for Colorcon. Victor has worked in quality systems for the pharmaceutical, chemical, and food industries. He has worked at Colorcon for more than 25 years in quality and facility manager roles, and he was onsite during the 2017 storm and has led recovery efforts. And Victor is going to share some of his insight about the events of the storm and what has transpired since.

Amador: Hello, everyone. I am going to share three important aspects for a company that was affected. Although we had in place a good BCP – a business continuity plan – that included **communications**, it didn't work as well as they were expecting, and we had no one to call because we had no communication. We were stuck with no communication for about three months. Even though our corporate was great and we had a big antenna and we had satellite phones, still we struggled with the communication.

So I would like to invite some people here after we are done to think about maybe doing deeper research on what should the industry on the island go with – satellite or optical fiber? At the moment, we have no optical fiber, so we communicated by a microwave antenna. So, I think we should do some research on, which is more reliable for our industry – satellite or optical fiber?

Jumping to the other subject – **emotions:** Wow, this was not written into our BCP and it really shocked me, because I am not a psychologist and I had to help people that really suffered because of this event.

Colorcon, here on the island – and on the mainland, too – has a really good program to assist our employees. However, we had no one to call to support our assets, our employees.

For example, one of our supervisors had a problem with his relatives. Two of his cousins lost their houses. Both of them had two kids. So this guy has to take care of these two ladies and four kids who had lost everything – no food, no clothes – and he had to take care of them himself in his house. He was struggling with no fuel, no nothing. So he was crashing down.

Another supervisor that we had – he had been working for Colorcon for 40 years – his family in Texas were asking him to move. He did not want to go, so he was very much asking us what was what, and he was crashed down and crying ‘what should I do, I don’t know. My son wants me to go.’ And this really confused him. So, his productivity went down. And again, we had no one to ask what to do with this guy, because every therapy office in that area was closed.

And then lack of **food and water**: We had water for maybe two days of work, but this takes more than that. So after one month, two months, we still had no water – so no work. People were asking where to get food, where to get water, where to get fuel, and we had no answer. We had nowhere to go.

So, I would ask: ‘how can our companies here on the island merge and work together to provide this kind of support to our employees?’

And finally **planning**: We did not have adequate information on how to handle unregulated behavior of a group of people in crisis. This was critical because we were in a day-to-day planning environment, and not having this created chaos in the company and for almost everyone here on the island, because we had no way to enlist the main services: electricity, water, fuel, and phones.

So we, the supervisors, were asked about what to do, what was the plan? We did not know. We did not have the right answer because we had no one to go and ask. So that created frustration and anxiety.

I hope this is not the end, this is the beginning for us on the island. We need to start thinking about having a BCP not only for people in corporate on the mainland, but also a local BCP to communicate and start doing stuff for our people and our companies here on the island.

Peters: Thank you, Victor. If you can just share briefly where your facility is located and its present status in terms of power?

Amador: We are located in Humacao. That area got affected very badly, and let me say we still have no power. We are using power generators and just surviving there. We are an auditor company in GMP and we are doing fine. But still we have to do some repairs, and people are still struggling because we have no electricity. They don’t know when they are going to even have a bath. The power company keeps promising and promising, so we are looking forward to getting electricity again.

Peters: We all wish it comes back very soon. Our next panelist is Dante Disparte, who gave a very enlightening presentation just a few moments ago. He is founder and CEO of Risk Cooperative and he discussed a number of the challenges that we are facing, and he tried to outline some of the opportunities, some of the actions we should take.

My first question for Dante is, in light of budgetary limitations, how does the government or regional development authority balance planning for a worst-case disaster? I am going to be going to BIO in a few weeks and it is filled with regional development authorities who are trying to bring pharma companies to their region. But they are talking about tax breaks and their employee base, and are not necessarily talking about what they do for disaster planning.

Disparte: I think the **budget question** really becomes sharply focused here in Puerto Rico. The island’s GDP in a good year is about \$100 billion, and right now Puerto Rico is upside down by 150% of its GDP. You take the public debt of \$73 billion, you take the \$94 billion reconstruction estimates, and you are upside down. If this was a home mortgage, we would be bailing out water in our basements or first floor for quite some time.

Disaster preparedness then – and how does the business community get off the sidelines, and how do these plants that many of the pharmaceutical companies operate, how do we become an extension of that civilian line of defense? And I love that the panel has really brought home what is often an abstract subject of risk and complexity of these issues and brought it down to the human level.

How do you ask first responders to pick up? How do you ask your staff to come to work the next day when they are affected at a level completely different and distinct?...

I think in that complex world, we had to have skin in the game from the corporate line down to the civilian line and really drive this kind of model to resilience where it says, 'the sidewalk in front of my office or building or store is broken and the city cannot fix it. Isn't it a part of our corporate role to get off the sidelines and put a little bit of that capital to bear?'

Unfortunately, Puerto Rico – and broadly this question of preparation – we had so many near misses on the island over many, many decades that we probably got a little comfortable. And hurricanes, unlike many other disasters, are the ones where we can see them coming and we can call it.

Katrina – simple case in point: There was enough planning to warn, and there were whole parking lots full of buses that went under and that were not deployed because the line of ownership was blurred between: Is that a public good? Is that a private good? And so we step off the side.

So, the assets we have to preserve the most when we are challenged like this are people. And I am glad that we have Victor and other panelists who have brought that message home.

Peters: But let's look at what some of the **corporate responsibilities** are then – obviously very bottom line focused. So how do you balance your business continuity planning with your corporate planning?

Disparte: All too often companies – and that was the narrative that I gave with my earlier remarks about "maximizer" versus "optimizer" – too much of the corporate operating model is driven towards profit maximization and as a result we tend to only do things that can be measured and rewarded in quarterly cycles.

Pre-investing in resilience and having a type of agile supply chain that Biogen just spoke about – that requires long range capital. And the reward is not just that you would avoid the risk. The reward is that the resilient organizations are the ones that can spring back.

Globally, last year was a \$300 billion to \$500 billion year, in terms of disasters – the worst ever recorded. And yet we consistently found communities in flood prone areas are under penetrated with flood insurance in low double digits: 11% in Houston – California very, very trivial penetration of earthquake insurance, for example. Where do all those costs go? They go to the public.

So, for every dollar that the private sector does not pickup – whether directly on company balance sheets or in the insurance market – you and I as taxpayers are paying. And so there is an interesting statistic that is worth sharing and I think it ought to re-inform how companies think about strategy and investing in risk resilience.

For every 1% penetration of insurance, there is a 22% taxpayer reduction in risk. Because again, if you think about it in scale: who is paying for Puerto Rico's reconstruction effort? Recently FEMA's administrator is joining the calls for \$50 billion or more to be deployed on the island. That's ultimately a taxpayer funded obligation affecting sovereign debt, affecting things elsewhere.

So private sector capital has to be the first line of defense, and we have to show that the communities that we are all part of as corporate citizens, we are not going to let them drown while the business stays afloat.

Schoneker: I want to take off on an idea I was thinking about as I heard Victor's comments and I talked a little bit earlier about it. You talked about what can we do on the island to **form a network of companies** here, with the new problems that you have, where you can come up with ways of solving this kind of communication issue in the future, unlike what you have done in the past?

And I was wondering as I was thinking about that: 'Well, OK, that sounds like there is a gap there that needs something. And I got to thinking we should have some sort of guideline that can help with this. And I was thinking maybe this is an area where IPEC could help. Many of our member companies are here in the island, and maybe we can act.

I am just throwing this out as an idea, guys. I haven't talked with the executive committee about it. Maybe we can act as a place or a forum where some of that discussion can take place. And I would like to get your thoughts about: 'What if we formed a committee under IPEC with all our members who are here on the island – and you guys on the island form the committee, not up in the US – and figure this out? And find out how the members of IPEC can set some standards on the island about how you would communicate in a situation like this? What kinds of networking needs to be in place? Is there a meeting place everybody goes to at a certain point to figure out what is going on?'

I don't know, there are a lot of thoughts about that. But maybe we can form something like that on the island with our members. Then start inviting in all the other companies who are not members, saying, 'how could we do this?' Because if we don't have a forum for that discussion, it is going to be a great idea talked about in the panel, but it is going to be very difficult for something to actually take place.

But since we already have this great network of neighbors, users, and distributors – many of which are here already – who went through this and are living with it, maybe we can use that network. And I am just throwing it out for us to all think about going on from here. Not that it is a plan, but something for us to talk about. Victor does that sound like something that would meet what you were thinking?

Amador: One thing that you brought in, David, is not only the status of the main services like electricity, as I mentioned before – employees were asking about electricity because that brought so much frustration. Not knowing if our customers were ready, or up and running, created a lot of confusion in our company. At least having some central place where we can find out what the status is and what is going on with the essential services on the island would be a big help to us – for the company as a business, and for our employees.

Schoneker: I think this is the thing that you and others on this panel have really brought to our attention that most of us haven't really thought about. We all have BCP plans for equipment and procedures and all that kind of stuff, but the people side of it has not always been part of this. Today's presentations have really brought this point home.

You had mentioned: 'How can the private sector here step up?' And I am thinking that one of the things we do at IPEC is identify a need where there is a gap – a need for a policy, or a guideline, or something else – and we as an organization for excipients have always found a way to fill the need when we have identified the gap.

And it sounds like this is an area of need that many of us care about. Maybe we can work together as the private sector and with our colleagues at FDA, who we get along with so well anyway, and see how we can connect the dots.

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Updates in Brief

UNITED STATES

CMC/REVIEW

FDA/Duke Public Meeting on Drug Shortages

FDA, together with the Duke Margolis Center for Health Policy, hosted a [public meeting](#) for stakeholders to discuss strategies and solutions for minimizing the harm caused by drug shortages. More than eight hours of the event were recorded and published online, along with: • the discussion guide • the agenda • participant biographies, and • presentation slides. Gottlieb and Woodcock describe new efforts to address shortages in their [announcement](#) of the meeting, and encourage the public to share their thoughts through the [public docket](#), which will be open until January 11, 2019.

Generic Drug Product-Specific Guidances

FDA [announced](#) a new set of product-specific guidances to support industry in identifying appropriate science-based methodologies and evidence for developing generic drugs. The batch contains 63 product-specific guidances, including 22 new guidances and 41 revised guidances. Of these, four are new draft guidances and 31 are revised guidances for complex drug products, including 23 products that, to date, do not have generic competition. The FDA has issued more than 1,600 product-specific guidances since 2007.

USP Proposal on Continuous Manufacturing Standards

The USP Quality Standards for Pharmaceutical Continuous Manufacturing Expert Panel published a *Stimuli* article in [PF 44\(6\)](#) that discusses and reviews what it believes “is the first attempt towards standardizing the vast terms and definitions used in the domain of PCM.” Topics include: • terms and definitions • material property characterization for PCM applications • risk management and statistical tools, and • regulatory considerations.

USP Proposal on Physical Stability Guidance

In another *Stimuli* article, also published in [PF 44\(6\)](#), the Physical Stability Joint Subcommittee is proposing that USP consider providing guidance regarding factors involved in the physical stability of pharmaceutical materials and dosage forms. The authors request feedback and comments from stakeholders. The article provides: • outlines of existing guidance • a working definition of physical stability • a chart of common types of physical instability • a list of common risk factors and analytical testing challenges, and • recommendations on building an appropriate control strategy.

GMP/INSPECTION

Commissioner on NIPP for Injectables

FDA Commissioner Gottlieb provided a [statement](#) on the steps the agency is taking to strengthen and modernize the oversight and reporting of inspections for sterile injectable drugs through its New Inspection Protocol Project (NIPP). FDA’s plan is to implement the series of inspection protocols to cover all dosage forms within the next two years. [See [IPQ September 28, 2015](#) for more on the development of NIPP and [IPQ October 22, 2018](#) for an update on FDA’s current drug inspection and compliance initiatives including NIPP.]

FDA ARB/Valsartan Impurity Q&A

FDA [published](#) a Q&A for impurities found in certain generic angiotensin II receptor blocker (ARB) products, including valsartan, losartan and irbesartan. An FDA [website](#) contains the most current information about the affected products.



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EUROPE**CMC/REVIEW****EC Q&A on Safety Features**

The European Commission published an updated frequently-asked [Q&A](#) (Version 12) regarding the implementation of the rules on the safety features for medicinal products for human use. The 28-page Q&A includes definitions, requirements, and exemptions addressing unique identifier and anti-tampering elements of drug labelling and packaging.

EMA on Non-Genotoxic Impurities

EMA published a draft reflection [paper](#) on the qualification of non-genotoxic impurities (NGI). Key considerations of the paper include: • integrated risk assessment • dose considerations • 'structure activity relationships to evaluate both the pharmacological and toxicological properties of the NGI • use of pharmacological and toxicological databases • *in vitro* approaches, and • qualification of the NGI at the specified level where no adverse effects are expected.

British Pharma Association on EC Brexit Agreement

The Association of the British Pharmaceutical Industry (ABPI) [commented](#) on the European Council's November [endorsement](#) of the agreement on Brexit and the UK's [Political Declaration](#) setting out the framework for the future relationship between the UK and the EU. Recognizing the significance of the development, ABPI Chief Executive Mike Thompson said: "The terms of the deal mean that medicines will continue to reach the patients who need them when the UK leaves the EU in March ... It also includes the 'possibility of cooperation' between the regulators, the MHRA and the EMA."

GMP/INSPECTION**EMA Guideline on Water Quality**

EMA published a new [guideline](#) on water quality for pharmaceutical use to reflect changes in the European Pharmacopoeia, that include: • a revised monograph for water for injections allowing the possibility to use methods other than distillation for producing water of injectable quality • a new monograph for water for preparation of extracts, and • the suppression of the monograph for highly purified water. The deadline to submit comments is May 15, 2019.

INTERNATIONAL**CMC/REVIEW****ICH November North Carolina Meeting Results**

ICH published a [summary](#) of its November meeting in North Carolina, USA. The summary: • highlights progress on new and existing ICH guidelines • describes training as a key to successful implementation, and • notes the importance of understanding the level of members' implementation of ICH guidelines. It was the first face-to-face meeting of ICH's expanded Management Committee, including representatives from the agencies of Singapore, Korea, and China and from the associations BIO and IGBA. ICH now has 16 members and 28 observers. Iran's regulatory agency was approved as an observer by the Assembly at the meeting. [See *IPQ September 6, 2018* for an *in-depth* review of how ICH is evolving.]

GMP/INSPECTION

Five More EU Member States Cleared for US-EU MRA

The US cleared five more EU member state inspectorates for inclusion in the US-EU Mutual Recognition Agreement (MRA) in November – Belgium, Denmark, Estonia, Finland, and Latvia – bringing the total to 20 that have been reviewed and approved. The [MRA](#) provides for sharing of and reliance on inspection reports and related information and reduction of surveillance inspection redundancy between the regions. FDA expects to complete its capability assessment of all EU inspectorates by July 2019.

Canada on CETA GMP Protocol and Mutual Recognition

In a [report](#), the Government of Canada summarized a meeting of the Joint Sectoral Group on Pharmaceuticals. Topics included: • the Comprehensive Economic and Trade Agreement (CETA) GMP Protocol and related administrative arrangements • recognition of the Active Pharmaceutical Ingredients Program under the CETA GMP Protocol on Pharmaceuticals, and • Canada’s proposal on a mutual recognition agreement for drug facility inspections in third countries. Six administrative arrangements to facilitate the effective implementation and monitoring of the CETA GMP Protocol were approved in principle and are expected to be adopted early in 2019.



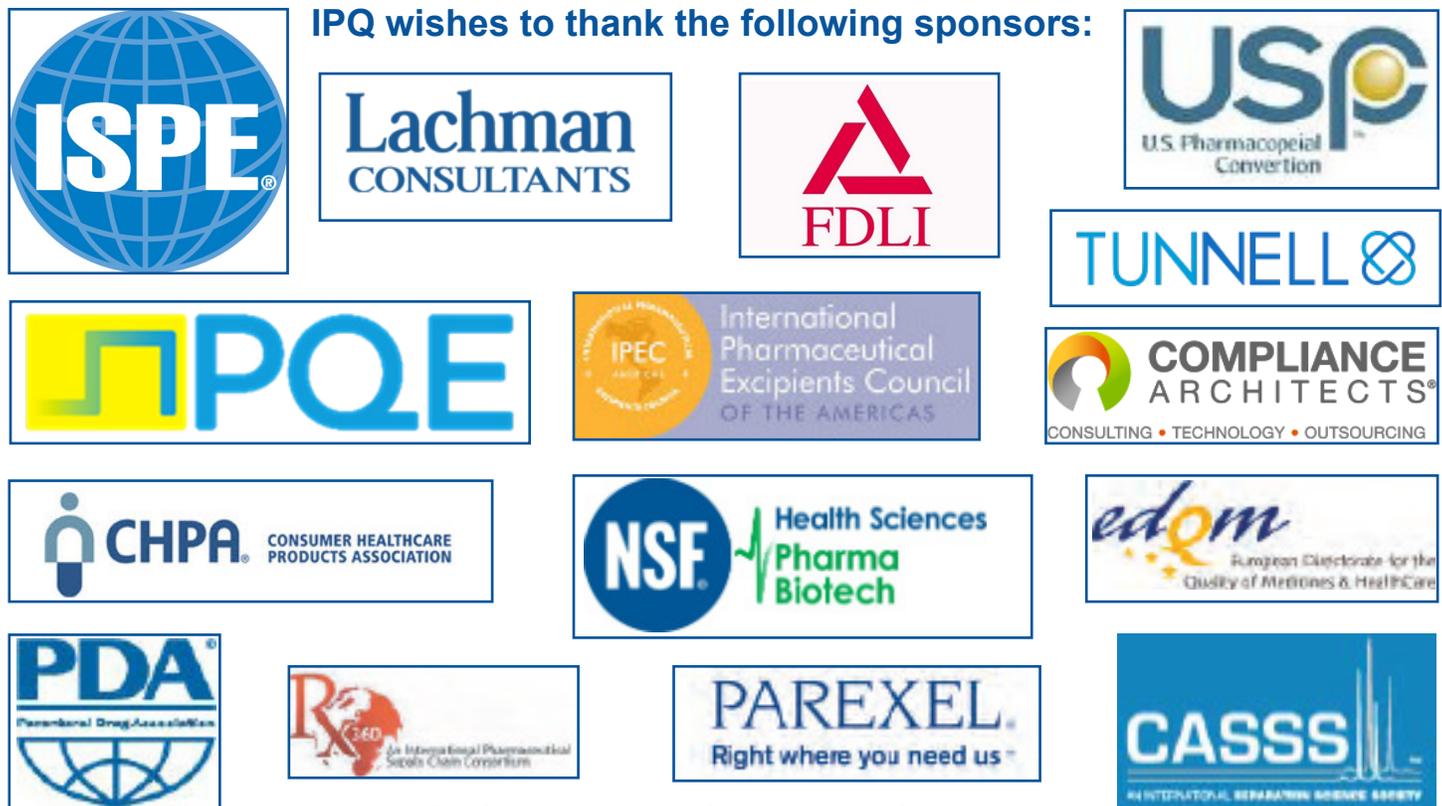
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FDA DRUG GMP WARNING LETTERS

The following are the drug GMP warning letters posted by FDA during September and October categorized into U.S. and International. The main areas of concerns are listed along with links to the warning letters themselves. Included is a review of the letter's most noteworthy features.

UNITED STATES

Facility	Inspection	Letter Date	Product Type	Areas Cited
Vital Rx dba Atlantic Pompano Beach, Florida	June/July 2017	September 26, 2018	Compounded	<ul style="list-style-type: none"> ● non-sporicidal cleaning agent ● endotoxin testing ● nonpharmaceutical grade filters ● sterility assurance ● environmental monitoring ● equipment condition ● cleaning procedures ● media fills

The warning letter began with an annotation recognizing the sale of the firm approximately one month after the inspection. Vital Rx ceased drug production on the final day of the inspection. A voluntary recall of all lots of injectable drug products was immediately implemented by the new ownership. The Florida Department of Health ordered an emergency restriction of the sterile compounding permit until reinspection could confirm product safety. Vital Rx has not provided a response to FDA regarding the inspection findings.

Vital Rx did not perform endotoxin testing for their intrathecal finished drug products. The firm used nonpharmaceutical grade filters to sterilize drug products, which bore the manufacturing label: "Do not use this product for direct patient care applications; it was designed for laboratory use only." Observations of poor environmental monitoring, nonrepresentative media fills, and six observations related to condition of equipment and cleaning were included in the letter.

Facility	Inspection	Letter Date	Product Type	Areas Cited
Prescription Labs dba Greenpark Houston, Texas	October 2017	October 26, 2018	Compounded	<ul style="list-style-type: none"> ● gowning ● nonsterile cleaning agent/wipes ● ISO certification ● smoke studies ● facility design ● media fills

Personnel at the Greenpark facility were engaged in aseptic processing with exposed skin and nonsterile garb within an ISO 5 area. Use of nonsterile wipes and cleaning agents was observed. The certification of the ISO 5 areas was inadequate because there was no evidence it included non-viable particle counts. Smoke studies under dynamic condition were not conducted.

FDA could not evaluate some CAPA for lack of information such as timelines and revised procedures. Other remediation documentation gaps included lack of receipts or COA for new cleaning products and lack of personnel training logs.

CAPA deemed deficient by FDA included Greenpark challenging the requirement to use sterile wipes in the cleanroom because the Texas State Board of Pharmacy only requires lint-free wipes. Similarly, the company claimed it was in compliance with Texas airflow smoke testing, which FDA considered inadequate because it was not conducted under dynamic conditions.

FDA noted that Greenpark failed to use biological indicators during sterilization of finished drug products to demonstrate sterility capability. Facility design regarding ISO air quality classifications was not appropriate to prevent ingress of less quality air. Finally, media fills were not conducted under the most challenging or stressful processing conditions.

Facility	Inspection	Letter Date	Product Type	Areas Cited
I. Shay Cosmetics Carson, California	November/ December 2017	October 29, 2018	Finished	<ul style="list-style-type: none"> ● OOS investigations ● quality unit ● stability testing ● component testing ● release testing ● repeat violations

FDA referenced similar CGMP violations and observations from previous inspections in warning and untitled letters going back to 2008.

The first citation highlighted in the letter was for inadequate OOS investigations, for which there were three detailed examples. FDA noted the firm's:

- plan to change specifications to meet test results without scientific support
- labeling on hydrogen peroxide bottles that stated: "If the bottle expands, don't sweat it; it's natural,"
- failure to validate the water supply.

FDA sought a comprehensive, independent assessment of the overall systems for investigations and a retrospective assessment of all drug products within expiry to determine whether they meet standards.

Failure to establish a quality unit and procedures to approve or reject all drug products was the second citation in the letter. On instructions from the CEO, the quality unit made decisions to release products that did not meet critical quality attributes and for which passing results were reported on the COAs.

The observation included for the stability citation was the assignment of a two-year expiry to a product even though lots failed to meet specification in multiple instances. During the inspection, the CEO indicated that failing test results were not necessarily indicative of product stability. FDA requested all OOS stability test results from the past five years with comprehensive related information.

Failure to conduct at least one test to verify the identity of components was the fourth citation. I. Shay relied on unqualified supplier COAs. According to the firm's procedure, the strength of the API would be "extrapolated" from finished product testing, which did not occur. The fifth citation was for failure to conduct identify and strength testing of the active drug substance prior to release. FDA requested a list of all products for which testing had not occurred and a detailed plan for how the testing will be done including timelines.

The warning letter included the links to six relevant guidances and a section iterating the responsibilities of contractors regarding CGMP. FDA listed the previous communications and inspections, specifically noting that "these repeated failures demonstrate that your facility's oversight and control over the manufacture of drugs is inadequate." In view of these repeat violations, FDA strongly recommended engagement of a consultant and independent assessments of the cited areas.

Facility	Inspection	Letter Date	Product Type	Areas Cited
Product Packaging West North Hollywood, CA	March 2018	November 2, 2018	Finished	<ul style="list-style-type: none"> ● DEG testing ● component testing ● written procedures ● process control ● water control ● equipment records ● QC unit

The warning letter's lead citation involved the failure to conduct identity tests on incoming materials – significantly incoming glycerin lots to determine whether diethylene glycol (DEG) or ethylene glycol (EG) was present. Product Packaging West was relying on unqualified supplier COAs without their own testing.

Lack of an ongoing program for monitoring process control was the next concern addressed. The firm lacked process validation studies for its OTC products. In addition, the water procedures it was using were both inadequate and not followed, and records for cleaning, sanitizing and inspecting the water system could not be provided.

The final citation involved the firm not having written procedures for numerous responsibilities of the quality unit, including complaint investigations and approval or rejection of labeling, components, in-process materials, and finished drug products.

FDA requested the firm's new SOPs and extensive information around the DEG testing and water systems including risk assessments for products already on the market. Links to DEG, water and several quality guidances were included, as well as the recommendation to engage a third-party consultant. The warning letter included a labeling compliance notification as well that "continued listing of the ingredient in this manner would render your product misbranded", as the firm used the subjective "may contain" rather than the required "contains" language regarding Yellow No.5.

Facility	Inspection	Letter Date	Product Type	Areas Cited
Surmasis Des Moines, Iowa	February to March 2018	November 6, 2018	Finished	<ul style="list-style-type: none"> record review outlier tests QC Unit batch records data integrity

Lack of quality unit oversight and data integrity were the principle sources of the observations included in the warning letter. The quality unit had been using a procedure which allowed for OOS results to be invalidated as outliers when investigations failed to identify a root cause or laboratory error. Over a page and a half, the warning letter addressed the use of outliers and proposed the next steps the firm should take.

Batch records did not record all pertinent data. For example, electronic data logs did not record excursion limit alarms. There was no evidence these excursions were investigated. Laboratory records were similarly cited for not including all data. There were several occasions of additional testing revealed by the audit trails which were not reported on a number of products. The system controls allowed analysts to create vagaries around the samples and corresponding data.

Aspects of the long form data integrity remediation outlined in the warning letter overlapped with requests regarding other deficiencies such as:

- comprehensive investigations
- risk assessments, and
- management strategy that includes a detailed CAPA and interim measures.

Facility	Inspection	Letter Date	Product Type	Areas Cited
Mylan Morgantown, West Virginia	March/April 2018	November 9, 2018	Finished	<ul style="list-style-type: none"> cleaning cross-contamination OOS investigations change control QC unit repeat violations

The warning letter to Mylan extensively detailed multiple observations for each of the three citations included in the letter. The remediation steps requested by FDA were equally detailed. The letter included a section highlighting the repeat nature of the observations at multiple Mylan sites worldwide since 2015. Two further sections on quality unit authority and quality unit guidances declared that the quality unit was not fully exercising its authority and the quality systems were inadequate, respectively.

The cleaning and validation program for manufacturing equipment to prevent cross-contamination was the first area addressed by the letter. Observations included visible contamination on equipment classified clean by multiple checks and rechecks, cleaning swab failures detected but not remediated, and a further half dozen procedural or validation failures.

Failure to adequately investigate OOS results and process deviations was addressed next. The letter included three examples:

- repeat violations of invalidated OOS results without justification
- blaming inexperienced operators in lieu of more scientific justification, and
- continuing to manufacture and release a product with known OOS trends for more than two years up to the time of the inspection.

In many cases, Mylan failed to use the change management system for significant changes. Changes in blend size, formulation, and manufacture of drug products were not evaluated consistently, appropriately, or thoroughly before execution. Furthermore, numerous batches with major process changes were not included in the stability program. Specific examples included products recalled for dissolution failures with unvalidated process changes. FDA concluded that Mylan’s lack of rigorous oversight of manufacturing changes continues to be a major factor in the unexpected variation observed in drug products.

Among the guidances cited in the letter was FDA’s OOS investigations guide and five more around establishing and maintaining a quality unit. The letter concluded with standard language around engaging a consultant and timelines for communication by the firm.



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EMA GMP NON-COMPLIANCE REPORTS

The following are the drug GMP non-compliance reports posted by EMA from November listed by report date. The main areas of concern are noted and links provided to the compliance reports themselves. Included is a review of the report's salient features.

Facility	Inspection	Letter Date	Product Type	Areas Cited
Yibin Lihao Biotechnology Co. Sichuan, China	October 2018 (by Italy)	November 22, 2018	API	<ul style="list-style-type: none"> ● material extraction from animal sources ● cross-contamination ● state of facilities ● equipment ● component storage ● material traceability ● process control ● drying ● packaging

The active substance cited at the facility, crude heparin sodium, was derived from animal sources. The inspection identified 24 GMP deficiencies, of which seven were categorized as major in the following areas: ● risk of contamination ● buildings and facilities ● equipment ● storage of starting materials ● process ● materials management and traceability, and ● recovery of solvents.

Non-compliant manufacturing processes identified in the report were the extraction of substance from natural sources, finishing steps, and biological quality control testing. Under the heading of finishing, the report cited the physical processing step of drying as well as both the primary and secondary packaging.

Actions taken or proposed by AIFA, Italy's national medicines agency, were prohibition of supply and variations to existing marketing authorizations. No recalls were recommended.

Facility	Inspection	Letter Date	Product Type	Areas Cited
Qilu Tiahne Pharmaceutical Shandong, China	August 2018 (by Austria)	November 26, 2018	API	<ul style="list-style-type: none"> ● cross-contamination ● cleaning ● environmental monitoring ● sterilization ● process control ● equipment ● finishing ● packaging ● QC testing

The report prepared by Austria's AGES included numerous detailed observations. Four different noncompliant sterile B-lactam active substances in lyophilized and powdered form were cited in the report.

In total, approximately 30 deficiencies were observed. Critical and major deficiencies were identified in: ● the quality unit ● environmental monitoring ● cross-contamination control ● cleaning ● production areas ● equipment ● maintenance ● storage ● utilities, and ● quality oversight.

The established cleaning procedures in the weighing room were not suitable for the handling of highly potent substances to avoid cross-contamination. Environmental monitoring positions did not reflect the worst-case locations based on risk evaluation. Air sampling devices were not in use during routine production in at least two locations, and the air sampling equipment did not comply with the current state of the art requirements.

Inspectors reported several interventions performed by operators such the removal of discarded bottles and boxes and the forwarding of stuck bottles without explaining what specifically was done wrong. There was no exchange procedure of gloves during production and employees were observed tracking powder material throughout the clean room on their boots by walking back and forth through it. Inspectors saw a screw falling from a piece of equipment onto the floor that was not observed by operators.

Cleaning procedure failures included lack of logical sequence of operations, such as starting cleaning activities prior to removal of filled bottles from the conveyor belt awaiting stoppering or removal of all discarded bottles, which were un-stoppered. Other cleaning deviations included: ● reusing cloths ● not changing mop heads ● mix-up of cleaning activities between class A and B rooms, and ● lack of proper training.

AGES recommended withdrawal of the GMP certificate and noted other certificates seem to be affected as well. EMA should organize a multinational inspection in early 2019, the report states. To avoid product shortages until the next positive inspection outcome, it was proposed that a designated (qualified) person of the national manufacturer must be present on-site during production of all subsequent batches to ensure GMP compliance. Existing and subsequent batches would have to undergo extensive retesting to identify unknown impurities and secure sterility based on a confirmed statistical scheme.

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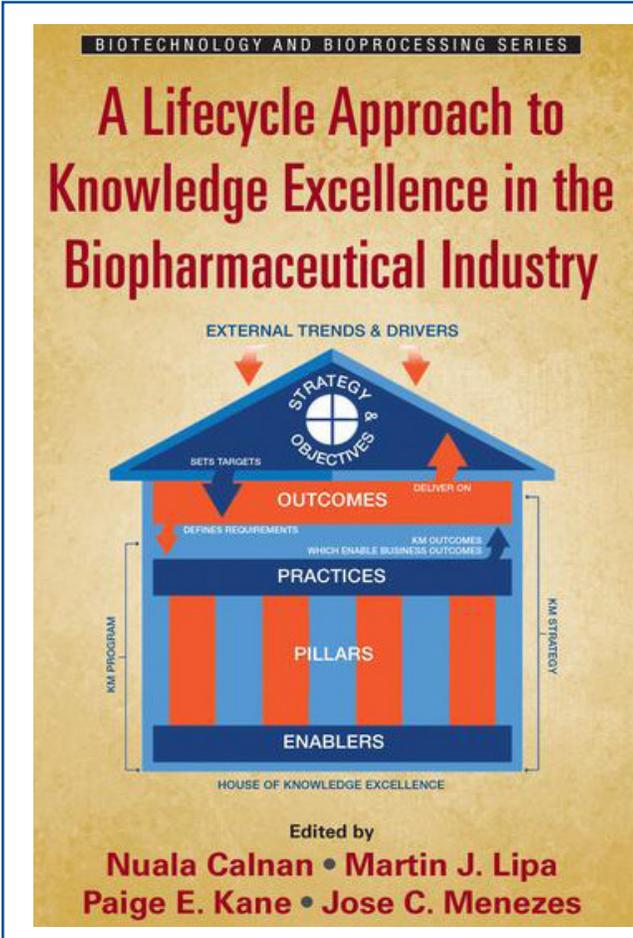
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OTHER FDA WARNING LETTERS ON DRUG-RELATED CONCERNS

The following is a listing of warning letters posted by FDA during November that went to nutritional supplement, OTC and cosmetic firms for misbranding, adding drugs to their products without approval, and/or not meeting the dietary supplement (DS) GMPs.

Company Name	Letter Date	Areas Cited
Delano. dba LifeLink	September 7, 2018	• DS GMPs • unapproved drugs • misbranding
Jinher	October 4, 2018	• DS GMPs
Netcos	October 29, 2018	• misbranding
United Exchange	October 29, 2018	• unapproved drugs • misbranding
Jack B Goods	November 7, 2018	• unapproved drugs • misbranding
MA Labs	November 7, 2018	• unapproved drugs • misbranding
Avalon	November 8, 2018	• DS GMPs



A Lifecycle Approach to Knowledge Excellence in the Biopharmaceutical Industry

June 16, 2017 by CRC Press 523 Pages - 144 Color Illustrations

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FDA DRUG RECALLS

The following is a list of the drug product recalls included in FDA's weekly [Enforcement Reports](#) issued during November. Listed are the generic names of the products, the dosage form, the manufacturer/recaller, the number of lots involved, FDA's classification, and the specific reason provided by FDA. The recalls are grouped by the general category of problem that caused them. The categories, not all of which are represented in any given month, are: • contamination/lack of sterility assurance • GMP/GDP • impurity • labeling/packaging • NDA/monograph compliance • particulate • potency/content uniformity • dissolution/stability, and • other spec nonconformance. Within the categories, the recalls are organized by class, with the most serious recalls (Class I) at the top.

Contamination / Lack of Sterility Assurance

Product	Recaller	Lots	Class	Reason
Oral spray	Silver Star	5	I	Microbial Contamination of Non-Sterile Product
Eye drops	Kadesh	All	I	Non-Sterility: Product manufactured under non-sterile production conditions.
Various inj.	Advanced Pharma, dba Avella of Deer Valley	6	II	Lack of Assurance of Sterility
Various solutions, inj. and eye wash	Pharm D	>300	II	Lack of Assurance of Sterility
Estradiol, testosterone pellets	Qualgen	~60	II	Lack of Assurance of Sterility
Various inj.	ICU Medical	8	II	Lack of Assurance of Sterility: Bags have the potential to leak.
Toothpaste	Medline	5	II	Microbial Contamination of Non-Sterile Product
Bevacizumab inj.	Avella of Deer Valley	1	II	Lack of Assurance of Sterility
Isosorbide tabs	Sandoz	4	II	Cross Contamination with Other Products
Nitrofurantoin caps	American Health Packaging	2	III	Cross Contamination with Other Products: This sub-recall is being initiated in support of the recall by the manufacturer (Sandoz) dated 11/1/18, which included lots that were repackaged by American Health Packaging. Sandoz stated that "These lots are being recalled due to the potential presence of unrelated ingredients (i.e. traces of active ingredients of benazepril, haloperidol and perphenazine), which were identified through a manufacturing investigation."

GMP / GDP

Product	Recaller	Lots	Class	Reason
Oral spray	Sprayology	All	II	CGMP Deviations: Products manufactured by contract manufacturer under conditions that could result in possible microbial contamination.
Irbesartan bulk API	Aurobindo	~40	II	CGMP Deviation: Presence of NDEA (N-Nitrosodimethylamine), a carcinogen impurity, detected in the active ingredient.
Oral spray	Silver Star	2	II	CGMP Deviations: Products manufactured by contract manufacturer under conditions that could result in possible microbial contamination.
Benzalkonium hand sanitizer	S.C. Johnson	2	II	CGMP Deviations: Product was released to market prior to microbiological testing.
Irbesartan tabs	Sciegen	~60	II	CGMP Deviations: FDA laboratory testing confirmed presence of an impurity, N-nitrosodimethylamine (NDEA) in product.

Impurity

Product	Recaller	Lots	Class	Reason
Cetirizine oral solution	Taro	3	II	Failed Impurities/Degradation Specifications: Unknown impurity higher than the specified limit was detected during routine stability testing.
Alprostadil inj.	Teva	1	II	Failed Impurities/Degradation Specifications: Out-of-specification results for impurities obtained during routine stability testing.
Lubiprostone	Takeda	1	III	Failed Impurities/Degradation Specifications: Elevated levels of a known impurity in the 20-month stability sample testing.

Labeling / Packaging

Product	Recaller	Lots	Class	Reason
Tesamorelin inj.	Tailor Made	~30	II	Labeling: Incorrect or Missing Lot and/or Expiration Date: Vial indicates a 1-year expiration date instead of a 6-month expiration date
Estradiol tabs	Janssen	3	II	Labeling: Incorrect Instructions: Instructions included for use with the Veridate dispenser contained instructions for the Dialpak dispenser.
Benzalkonium hand soap	Ecolab	3	II	Labeling: Label Mix-Up: The label on the product may not match the formula in the bottle.
Naltrexone tabs	Orexigen	1	III	Container Packaging Defect
Cetuximab inj.	Eli Lilly	1	III	Labeling: Missing label: Potential for missing primary container label on the vial.
Progesterone caps	Right Value	~30	III	Labeling Not Elsewhere Classified: Misbranding

NDA/Monograph Compliance

Product	Recaller	Lots	Class	Reason
Dietary caps	Epic Products	All	I	Marketed Without an Approved NDA/ANDA: Product contains undeclared sildenafil, tadalafil, and oxytetracycline – FDA approved drug products – making Euphoric an unapproved drug.
Dietary caps	Zero Xtreme	1	II	Marketed Without an Approved NDA/ANDA: Undeclared Sibutramine

Particulate

Product	Recaller	Lots	Class	Reason
Antacid tabs	L. Perrigo	5	II	Presence of Foreign Substance: Product found to contain metal particles.

Stability / Dissolution

Product	Recaller	Lots	Class	Reason
Clonidine tabs	Boehringer Ingelheim	1	II	Failed Dissolution Specifications: OOS results during routine stability testing
Clopidogrel tabs	Dr. Reddy's	1	II	Failed Dissolution Specification: Out-of-Specification results were observed for dissolution at 18-month stability testing.
Megestrol oral suspension	Breckenridge	6	III	Failed Stability Specifications: Out-of-Specification results obtained for particle size distribution during stability testing.

Other Spec Nonconformity

Product	Recaller	Lots	Class	Reason
Metoprolol inj.	RemedyRepack [mfg. Claris]	2	III	Failed pH Specifications: High out-of-specification results for pH were obtained during stability testing.
Metoprolol inj.	Baxter	~40	III	Failed pH Specifications: Upward shift in the pH of the solution within the shelf life of the impacted lots.



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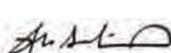
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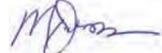
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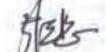

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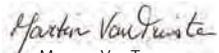

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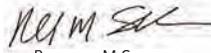

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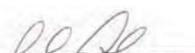

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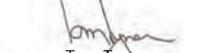

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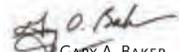

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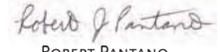

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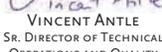

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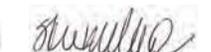

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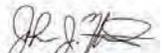

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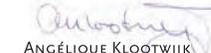

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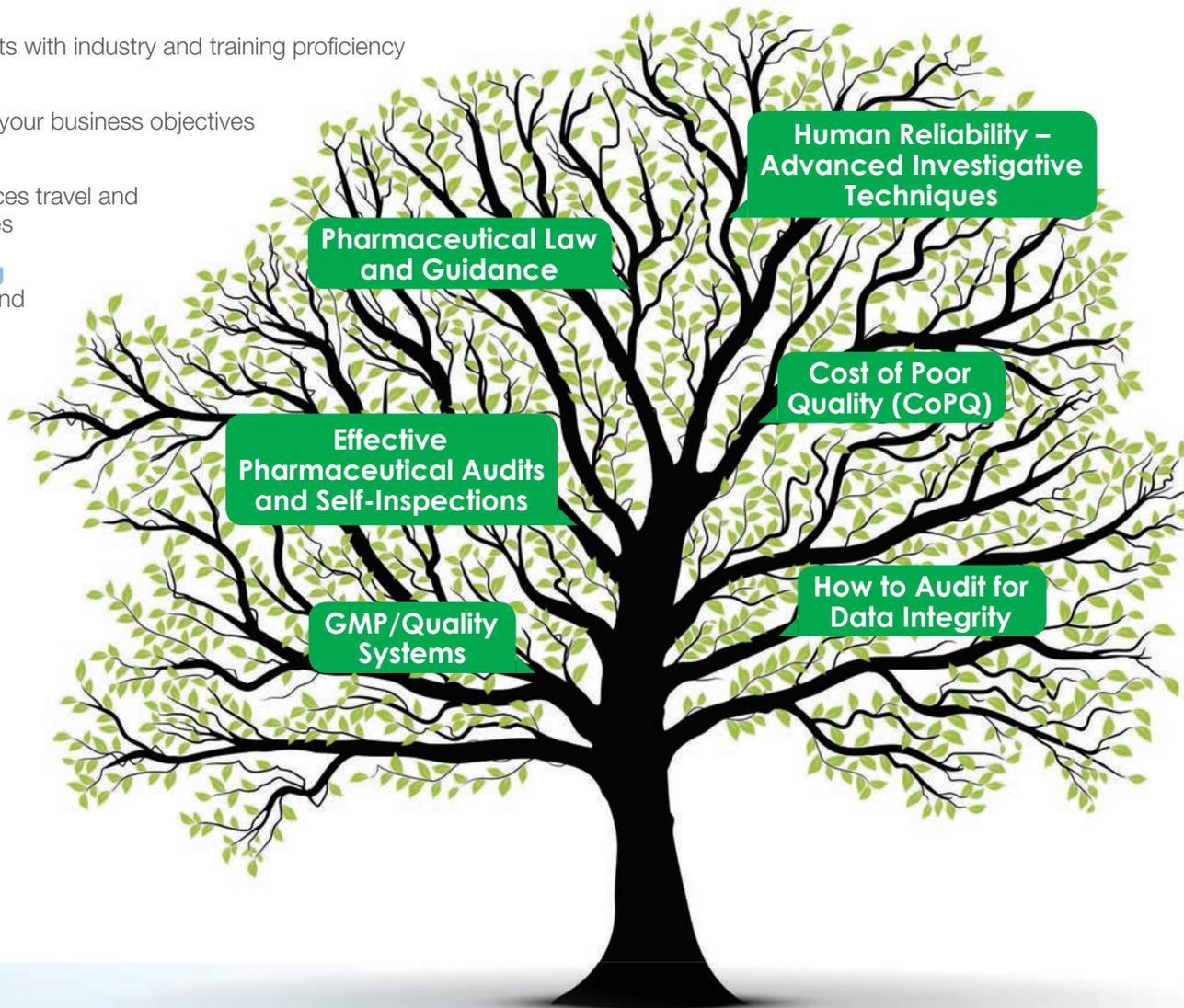
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