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Balancing Quality Assurance & Innovation in Pharma

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IPQ INTERNATIONAL PHARMACEUTICAL QUALITY
Inside the Global Regulatory Dialogue

BI'S EMMA RAMNARINE ON BALANCING QA AND INNOVATION

Editor's note: *This presentation write-up was prepared by the editorial team at International Pharmaceutical Quality (IPQ) and appeared in their publication "Implementing ICH Q9(R1) Will Entail a Heightened Focus on Integrating Knowledge into Risk-Based Decision-Making (Link: https://ipq.org/implementing-ich-q9r1-will-entail-a-heightened-focus-on-knowledge-management-and-risk-based-decision-making/).*

At the Pharmaceutical Regulatory Science Team (PRST) workshop on ICH Q9(R1), held at the Technological University Dublin in early June 2023, Boehringer Ingelheim US Biopharma Operations Product Management & Development Operations Head Emma Ramnarine shared her insights on balancing quality assurance and innovation in pharmaceutical manufacturing. She addressed: ● patient-centered transformation ● a watershed moment in her career ● understanding the drug shortage problem ● disruptive collaboration, and ● systems thinking approaches. Click here for the slides accompanying Ramnarine's remarks. She connected some of her remarks for the pharmaceutical industry to those made in the previous talk by Ed Hoffman, who was formerly the Chief Knowledge Officer for the US National Aeronautics and Space Administration (NASA). Formatting changes and other minor edits have been made for clarity by IPQ. Expressions of thanks to the meeting organizers/ attendees and disclaimers that the presentation represents the speaker's views and not necessarily those of their organization are not included.

Hello, everyone. Thank you, Ed [Hoffman]. That was really good. And I think you set me up well for my part, so I appreciate that.

What I am going to talk about is balancing quality assurance and innovation in pharma.

I picked this topic, and Ed touched on it too, because it sounds like a paradox, right? Because quality assurance is methodical, systematic. It takes time and has no room for failure. On the other hand, innovation is fast – experiment, fail, learn, and adapt. That is kind of what it seems like.

So, what I will talk about is, 'Is it really a paradox, or are the two mutually interdependent?' We will explore it together.

And then the other food for thought that I will plant with you right now, and we will come back to it: 'Is collaborative disruption the same as disruptive collaboration?'

Patient-Centered Transformation

We are in a time when there is this unprecedented convergence of medical knowledge, data science, and technology. At the same time, human and disease biology understanding is becoming increasingly unique, and it has brought us to a point of truly a different way of caring for patients.

When we talk about personalized healthcare, we have moved from the times of every patient receiving the same medicine for a particular indication to highly personalized care based on every single person's disease.

And then when you talk about our advanced therapeutic medicinal products, cell and gene therapies, patients are now integrated into the manufacturing and supply chain parts of medicines development and lifecycle of the medicine – not to mention when you look at generics and biosimilars. These are really broadening access for patients.

So where are we today? We are truly in the space of patient-centered transformation. That is what our landscape is. And I would say innovation is not just the front end – developing the medicines and bringing them to the patient is only one part of the story – there is more to the story.

Maintaining Control While Continually Improving

Aristotle, Socrates, all of them have said some version of this: 'The more I know, the more I realize how little I know.'

The important thing is to never stop questioning with that child-like curiosity that somehow we seem to lose, and it gets diluted as we move into adulthood. And that is not because of anything else other than getting tied down by procedures and systems, and we are taught and trained on those procedures and systems. So, we tend to stay 'within the box' in terms of our thinking and operation.

When you think about a product's lifecycle, it takes 10 to 15 years to bring it to commercial life, which is important. But it is only one-third of the story. This is the front end, which is achieving **product realization** and bringing the product to market. But as I said, it is only one part of a product's lifecycle story.

Another third of the story is about **establishing and maintaining a state of control**. And then the last third is about **continual improvement**.

All three of those are really important, and we cannot simply just bring a medicine up to commercial life and call it done. The medicine then has to then live in that commercial life and stay in a state of control and continual improvement.

Coming back to that paradox: How does one maintain, which implies one does not change, while improving, which implies you have to change? So that is the paradox in terms of, 'How do you do the second and third thirds well in a product's life?'

The Watershed Moment

As Ed mentioned, stories are super important. There was a defining moment, an inflection point, for me in my career.

We got a complete response letter from the FDA for a product that had been in its commercial life for 20-plus years. The complete response letter was: 'This product has been in commercial life for that long, and yet, the analytical methods and technologies are what you had launched it with. They did not get improved. You need to update the control system.' And it was not just this product. We needed to update the control system for all other commercial products.

I was heading up Analytical Science and Technology at that point. And so we said, 'all right, let's do this undertaking for all our commercial products' – only to find out that to make that update was easily five-plus years for each product. How could that be? How could it be that five-plus years is okay, from a patient's perspective, to make an improvement? That cannot be right.

The reason for that was simply that when we make a change to a product after it has been approved, it needs to be submitted to every country to get approval for the change. And that can take five-plus years, even if it is the right thing to do and makes complete sense.

And so, therein lies the paradox. All health authorities want continual improvement, companies want continual improvement, and yet it is so hard, and yet there is not an incentive to improve.

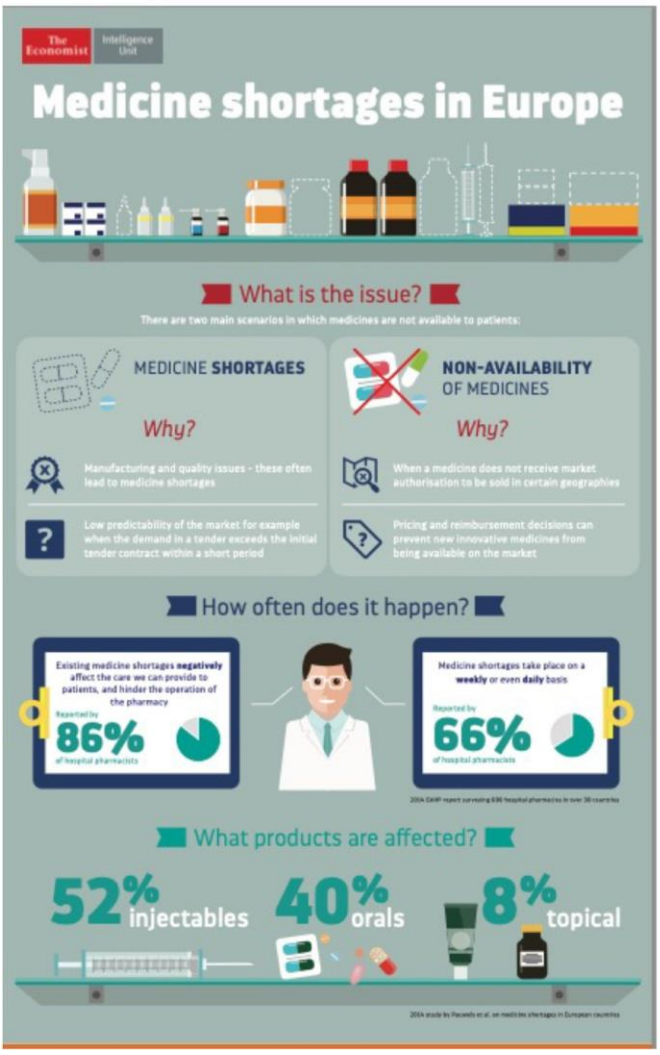
Drug Shortages Increasing Globally

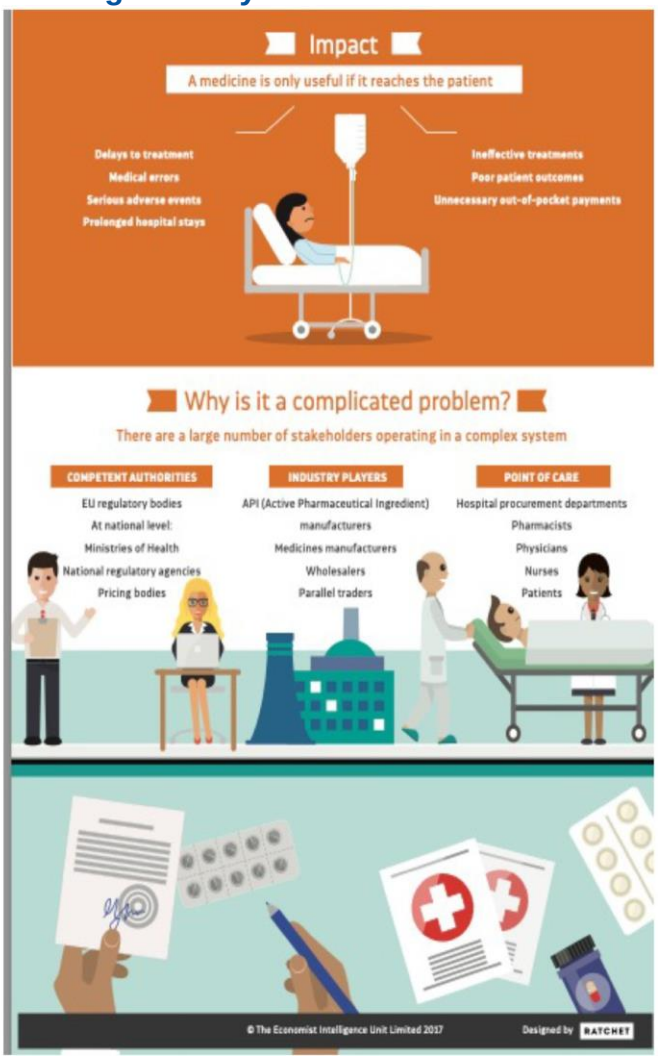
At the same time – this was back in 2011-2012 when we started down our journey – an increased focus on drug shortages being a global problem had also started coming through. There was an increasing spotlight on medicines not being available. Simple medicines like amoxicillin, saline, paracetamol – things that you would not think would be in shortage – were not available.

And this was an infographic that the Economist Intelligence Unit put out around drug shortages ***[see next page].*** The intent is not to read here, but it is a great infographic. You can find it online, but this was back in 2014. It talked about 'Why is this an issue? Why are we having drug shortages?'

And the answer was, well, we are having all kinds of manufacturing and quality issues. And those manufacturing and quality issues are causing drug shortages. I would say that 10 years later, the story of drug shortages hasn't changed, and that landscape hasn't changed. In fact, it has probably gotten worse than it was.

Drug Shortages Increasing Globally





Common, Unifying Objective

Let us go back to some of the basics, and I will come back to that infographic. Let's just get grounded on some basics that nobody will contest. Patients deserve to receive every dose of the medicine they need every single day, on time, every time. Does anybody disagree with that? Right, that is a fact. Patients need their medicine.

Here is another one, and this is a great quote from Louis Pasteur: 'Science knows no country because knowledge belongs to humanity, and it is the torch which illuminates the world. Science is the highest personification of the nation because that nation will remain the first which carries the furthest the works of thought and intelligence.'

Basically, what we are saying is that diseases know no borders, and science knows no borders. And patients do not care. When they need their medicine, they need their medicine. It doesn't matter which country they are in.

Another basic: there are a lot of stakeholders involved. It is not just companies and regulators. There are more stakeholders. I put a few on this slide, but I think there are more than these. It is a complex ecosystem, and we do need to take a moment to appreciate the complexity of this ecosystem. Because currently, no stakeholder now or in the future can solve this problem by themselves.

What is a reality is that every stakeholder tends to operate within their specific lane, within their area of remit. And Ed, thanks for pointing out what NASA did in terms of engaging stakeholders beyond NASA. I'll talk a little bit more about the theme of collaboration.

But all stakeholders in this picture want the same thing – an uninterrupted supply of safe and efficacious medicines. That is the common objective. Nobody will contest that here as well.

Understanding the Drug Shortage Problem

All right, so why is this a problem? I think partly it is because when we tend to operate in our respective stakeholder lanes, that causes a limited understanding of issues and challenges that each stakeholder faces within their own areas. What that also leads to is sometimes assumptions about other stakeholders and their processes, which may or may not be right.

There is really no common forum for all of these stakeholder communities to exchange with each other. So when you don't have the ability to exchange, that sometimes continues to perpetuate some of the assumptions or misgivings that might exist in each of the stakeholder groups.

And while every stakeholder group is working towards putting together solutions, those solutions may have blind spots because of the limited understanding of what happens in other stakeholder lanes.

Coming back to this, if everyone has the same objective of an uninterrupted supply of safe, efficacious medicines, why do we have this problem? Why are we having drug shortages? I love that we are doing this in an academic institution because the biggest thing I love about academic institutions is that you never stop asking why. You don't stop at the first why.

Why are there drug shortages? Due to manufacturing and quality issues. Why are there manufacturing and quality issues? And that five why's technique – sometimes you may go to 20 why's before you get to, how do we really solve this?

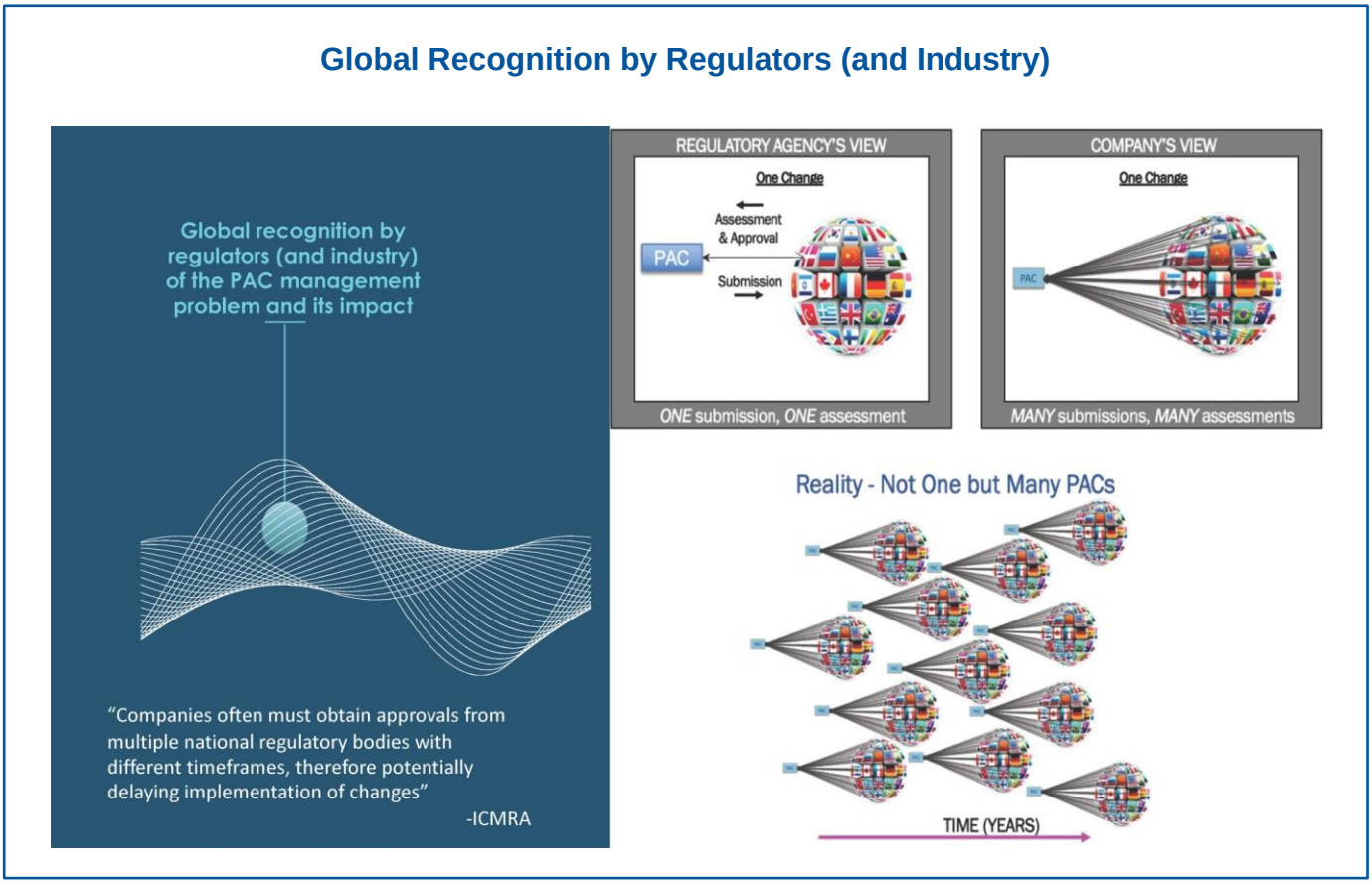
So I would say don't stop asking the why, even in your routine activities. Keep being curious, keep pulling that thread. I think my journey on this started because I started pulling the thread around drug shortages ten years ago.

One Product for One World

Here is the second paradox: the same product, the same indication, the same set of patients, the same change when we need to make changes, same technical assessments for the change, same risk basis – yet we need 100-plus approvals for that change if that product is marketed in each of those countries. Why? Why are our frameworks set up this way? They cause a lot of delays in making the needed timely improvements to products and processes.

Having said that, I want to provide a graphical view, and this is why I bring this up. I only picked two stakeholders here, but if you were to add other stakeholders, you will see different perspectives. On the top left is what may be the view from a country's standpoint, from a regulator's standpoint, when a post-approval change is submitted. From a company's standpoint, it is the same post-approval change submitted to all of the countries that need to approve it.

However, there is **not just one change**. Typically, global pharma companies – for those of you that are here from global pharma companies – may have up to 2000 post-approval changes in a year. So the picture at the bottom is what the enormously complex reality is.



Stakeholder 'Blind Spots' Being Addressed

Think about it from one stakeholder's point of view. It really is that regulators have a view of what is happening within their country, but they do not have a view of what the global supply chain looks like.

On the other hand, companies may have a view of what the global supply chain looks like, but they don't have a view of where each post-approval change is sitting in terms of its approval status in each country.

So talking about blind spots: Why it is really important for stakeholders to collaborate is because there are blind spots that different stakeholders have and you need to come together to talk about and overcome them collectively.

The good news is that there is now **more global recognition** of this problem. The International Coalition of Medicines Regulatory Authorities, ICMRA, has the PQKMS which is called the 'Pharmaceutical Quality Knowledge Management System' initiative. And it is acknowledging for the first time in a very, very long time over the years at a global level that the ability to not make changes is delaying implementation of needed changes. And by extension, it is delaying continual improvement and innovation.

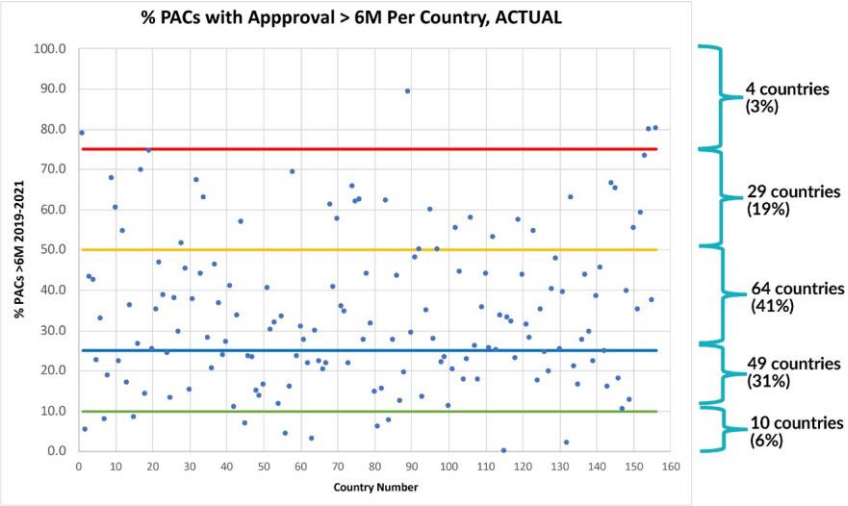
So the good news is that the awareness is there now. And the first part of every journey is having that common awareness.

Post-Approval Change Timelines

This is data that was collected over three years from 16 global pharma companies. Every dot in the graph represents a country and there are 156 countries there. This is the first-time data has been collected for 125,000 post-approval changes over three years, showing that only one out of 156 countries meets the WHO-recommended timeline of approving changes within six months – one out of 156 countries.

One in five countries is taking longer than six months for the majority of the post-approval changes, and it is very rare that any change is approved globally in six months.

Percentage Post Approval Changes (PACs) Approved



- 125,886 data points from 16 of the top 25 pharma companies for 2019-2021
- 1 of 156 countries met the WHO recommendation of no PAC approval exceeding 6 months
- 1 in 5 countries take longer than 6 months for majority of PACs

What that means is, until a change is approved in all the countries that need to approve it, it is simply not possible to implement it. The data tells a very compelling story about what the current state is. Anecdotally we knew this. It is not surprising.

However, the important point here is that with the data showing this, what is it that we need to do to have all of those dots at least below the 10% line? That would be a great step in the right direction. It would indicate that we are moving the needle towards driving continual improvement and innovation faster.

This data is going to be published soon, so look for it. This comes out of the One-Voice-of-Quality for Post-Approval Changes (1VQ for PAC) initiative, and it has been great to have the Chief Quality Officers from all of these companies not only submit the data but come together and speak with one voice.

Product Realization

All right, so going back to those whys. Why drug shortages? Because of manufacturing and quality issues. Why manufacturing and quality issues? Because of delayed improvements. Why delayed improvements? Because it takes a very long time to make changes. We have got to do something about this.

It is not enough to bring new medicines to market. I have said that before. We need to keep their supply uninterrupted.

In this picture ***(see slide #15)***, the CAR T cells are blue, and the tumor cells are red. The CAR T cells are attacking the tumor cells. This is a fantastic advancement in science, innovation, and bringing new therapies for patients, which is much needed. Absolutely.

However, it is not sufficient. How can it be that sometimes it takes nearly the same amount of time to make a change as it does to bring a new therapy to market? That cannot be right. That cannot be the space that our industry and our healthcare sector should be in, and accept as the norm.

We have to be able to have all three parts of the story work well in terms of a product lifecycle management, because that is what patients deserve.

Driving Continual Improvement to Maintain a State of Control

So coming back to that paradox, how do we drive continual improvement while maintaining a state of control? I would suggest to you that it is not a paradox. In fact, you need to drive continual improvement in order to maintain a state of control. I published a paper on this a couple of years ago.

There is new knowledge that we gain all through the commercial life of a product. Based on that new knowledge, we need to act. We need to make changes and improvements based on the new things that we have learned.

And in order to maintain that state of control, think about it like driving a car: If you keep driving and you don't maintain the car, it is going to break down. At some point, systems are going to break down, processes are going to break down, technologies are going to break down. You've got to bring in new and better, especially for a product that is living 20-plus years in its commercial life.

Today, that is not an hourglass ***[slide #16]*****,** that is a decade glass, in case of some changes. And that has got to change. We've got to move from years to weeks and months in making improvements.

Collaborative Disruption

So, allow me a little bit of philosophy here. In terms of where we are, per human nature, our **belief** often is that the world is a just place.

How we wish the world to be is the **delta** between what the current state is, and what we believe it should be.

And the **tendency** – this is the reality, and it is also important to acknowledge – is that we self-handicap ourselves and say what others need to do, as opposed to what we can each do individually in our lanes, and then collectively as a community across that healthcare ecosystem.

Change is necessary. I won't belabor that point. Incremental improvement is not going to be sufficient. Sometimes you really have to create a new path. And that path may not exist. Because if we are looking to go faster on the current path, that may not be good enough, and it may not get us to where we need to be. We may have to forge new paths in order to get to that new state.

Ed talked about this, **collaboration**. It is truly important to not only collaborate within the stakeholder communities that we are each a part of, but across those stakeholder communities. Because without that, we are not going to get to that end state.

So, **collaborative disruption**. I asked you to think about that term earlier. Here are some examples where stakeholder communities are coming together to speak with one voice to disrupt for good change. And stakeholders coming together to speak with one voice is really important in driving that collaboration and collectively driving innovation.

A couple of examples from WHO: the **Collaborative Procedure** for accelerated approvals by sharing and exchanging information on assessments and inspections that allows for faster approvals and avoid duplicative regulatory work. **Good Reliance Practices** from WHO is another example.

The **PQKMS initiative**, pharmaceutical quality knowledge management system initiative, from ICMRA. That is another one where regulators are coming together to talk about, 'How do we move differently?'

And from the industry side, an example is the **One-Voice-of-Quality for Post Approval Changes (1VQ for PAC) Initiative,** I talked about that.

These are examples of collaborative disruption within stakeholder groups. We need more of this. We definitely need more of this.

Science, Reliance, and Trust

And basically, at the bottom of all that, we are talking about science and we are talking about collaborating to have reliance among the different regulatory authorities.

The basis for that is trust – trust in the data on the science side, and trust in the decisions on the reliance side. So that trust is fundamentally really, really important. And going back to what Ed said around relationships and talking to each other and communicating, how do we build trust without coming together and having those conversations?

You cannot. You simply cannot, because then you are really only looking at procedures and what is written in the documents. And oftentimes that is not how innovation happens. It does not happen through procedures. It happens through collaboration, bringing ideas and partners together to exchange and solve.

And it requires a risk-based mindset. Risk management by all stakeholder groups.

Healthcare at an Inflection Point

Then COVID happened. And it slammed all of us into another watershed moment. It slammed all of us in the healthcare industry into another inflection point on a global scale that we had never before seen.

What did we have to do as a healthcare system? We had to respond to the crisis. And we did. We did a lot that should be commended and be proud of in terms of dealing with the crisis.

At the same time, new ways had to emerge. We really had to think about new ways of operating. And now that we are stepping into the post-pandemic space, more of those new ways of thinking and operating are necessary.

I will read a quote from Dr. Janet Woodcock. She said this about 20 years ago, it has been a while: She envisioned the pharmaceutical industry as a 'maximally efficient, agile, flexible pharmaceutical sector that reliably produces high-quality drugs without regulatory oversight.'

Well, a lot of new requirements and expectations have been added, and new solutions have been put in place. But they have been mostly with stakeholders operating within their own remit. And I would say it is not enough, and it is not good enough for patients. It really is not enough. Some might say the situation has even gotten worse over that time and we are far from the vision Dr. Woodcock laid out.

Systems Thinking Approaches

It is not enough for us to just learn new things and have a good learning environment. It is also important for us to unlearn some of the ways that we work.

Unlearning, I would posit to you, is harder than learning new things. Right? And so, we have to rewire and sometimes even just shed our current ways of thinking and working. That unlearning bit becomes really important if we have to drive toward this truly patient-centered transformation in new ways.

Systems thinking: Ed alluded to this. A system is a group of interacting interdependent parts that form a complex whole. Systems thinking is the process of understanding how all the components of a system influence each other as well as other systems.

I would say that even collaborative disruption is not enough. It really is time for **disruptive collaboration.**

Because that disruptive collaboration is what will truly put patients at the center. It is where each stakeholder needs to step out of the boundaries of their respective sub-part, and we need to come together to co-create solutions.

For disruptive collaboration, two things are important. One is that you have to actively seek **diverse viewpoints** with curiosity, going back to that scientific mindset.

And the second thing is that **healthy debate** is so necessary, without judgment. Because you have to be able to harness the collective power of that community. And that by default means that the power of any sub-part in that system gets diminished for the good of the collective whole.

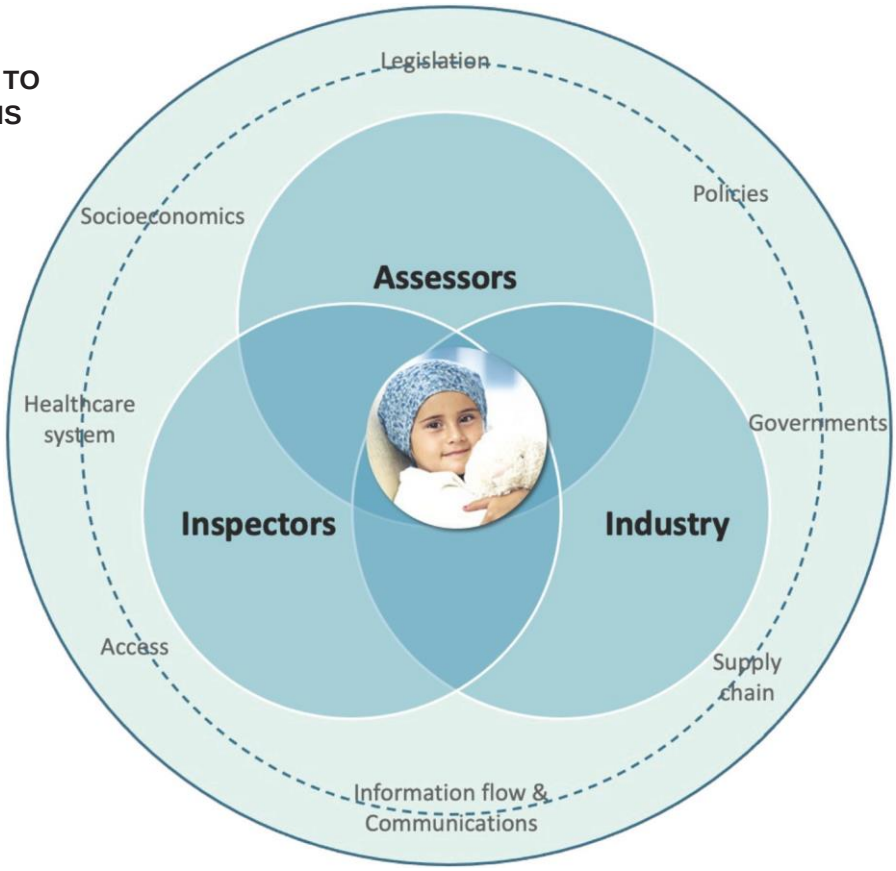
Because to harness that collective power, we need to come together and set aside any old ways, and any current ways, of thinking that might be impeding us.

Systems Thinking

FROM STAKEHOLDER-FOCUSED TO PATIENT-CENTERED SOLUTIONS

How to solve a Complex Problem

1. Everyone acknowledges and gets to a common understanding of the problem
2. Accept that no stakeholder alone can solve the problem
3. Decision-makers across stakeholder groups come together to agree on path
4. Collaboratively design and implement standard solutions



I talked about disruptive collaboration, in terms of those stakeholder communities interacting more with each other. But what other areas of disruptive collaboration need to be considered? Healthcare models, policy making, legislation change, information flows? This is a complex ecosystem, but it can be solved.

I would say it really is time for that disruptive collaboration because we can never be good enough or fast enough for patients.

Dr. Albert Tate had this quote that really resonated with me. ‘What if the COVID-19 pandemic wasn’t a test? What if it was a lesson and the test is yet to come?’

And I would say that disruptive collaboration is going to be the game changer. Right? And our patients deserve no less than that.
