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Optimizing the Value of Quality: Proactive Quality Management

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GSK (with Alexion at time of conference)*

Optimizing the Value of Quality through Proactive Quality Management

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Good afternoon, everybody. My name is Jane Wyatt. I am the Head of Quality for Alexion Operations. My business partner in operations is Maureen Larkin, who is taking part today and was on the 'Quality and Operations Partnership' panel. She is an excellent partner, so everything she said there is true. I am also ex-Wyeth Grange Castle, so there are a few of us here today.

It has been really interesting so far to listen to everybody, and you would think we all went into a room together and decided what to talk about. Because everything that Janet [Woodcock] and Lorraine [Nolan] and everyone so far has talked about will definitely resonate in my talk.

My topic today is to talk about how we can optimize the value of quality through proactive quality management. I have been a quality professional for 25 years. I have always been in quality, so I am a quality leader, but I would like to think that I am a quality business leader.

I spent the last couple of years getting to know a little bit more about how we operate as a business. I can now speak the same language as my finance partner, and he can speak mine.

Janet mentioned earlier that quality leaders sometimes cannot be considered corporate leaders, and I do feel that—sometimes, you are in the room and you can't speak their language, or you can't be an advocate for quality and the value quality can bring.

Instead, it might be a little bit more about inspections, a little bit more about metrics and lagging metrics. So, we need to turn the dial. And I think it resonates a lot with what we have talked about so far.

So today, I will talk a little bit, but not too much because you all know this, about understanding the value of quality. What is the cost of poor quality, just to give you some examples, and what is the value of having good quality.

And then, I will briefly touch on what a quality management system should be and what an effective, robust quality management system should be, then talk a little bit about what proactive quality management is, and what we can do to move the dial into proactive quality.

And then using proactive quality management systems, how in the industry – definitely myself and other quality leaders – we are trying to demonstrate that we can add value through proactive quality management.

Unfortunately, we have to talk in dollars to ensure that we can get approval and endorsement of these types of things – that by selling the value of quality we will get the endorsement and approval from the business.

Understanding the Value of Quality

So, the value of quality: There is good quality and there is poor quality.

Good quality includes prevention and appraisal – so the costs of your QMS, quality resources, QMR, maintaining your specs, QIPs [quality plans], training, and quality culture.

And then your appraisal is:

- your incoming inspections
- your process controls
- your audits
- your supplier assessments, and
- your analytical lifecycle management.

They are all costs that I have to put in my budget, and they are part of the cost of goods, so they are just perceived as costs to the company.

The things that cost money are the bad quality, which are the internal and external failures that we don't want to see. So:

- re-processing/re-work
- rejected batches
- low yield
- downtime of equipment
- the cost of deviations
- the cost of change controls.

External failures are product complaints, patient safety risk, and product shortage, dealing with all those issues. Also, the cost of our reputation that I will give some examples of, and the cost of health authority remediation.

So, if we have an inspection, and we have a 483 or major [observations] – the time and effort to respond, to right it, to fix the wrongs – there are huge costs associated with that. And then delays in approvals can have a market impact and cost to the company.

So, we want to get the balance right and we want to improve the good quality.

The Cost of Poor Quality

The **cost** of poor quality: So far in 2024, the FDA has had approximately 18 – and it is probably more now – drug product recalls. Drug shortages, as we have mentioned, throughout the world cost money. And then last year alone, almost a hundred 483s were issued. So that is the cost of poor quality.

What does that mean for companies? So, there is one company there, but there are so many examples. The company Momenta had a poor deviation CRL [complete response letter] and on the day of the issue, and the delayed approval of the product, their stock price fell by 20%. So there is a huge cost associated with that.

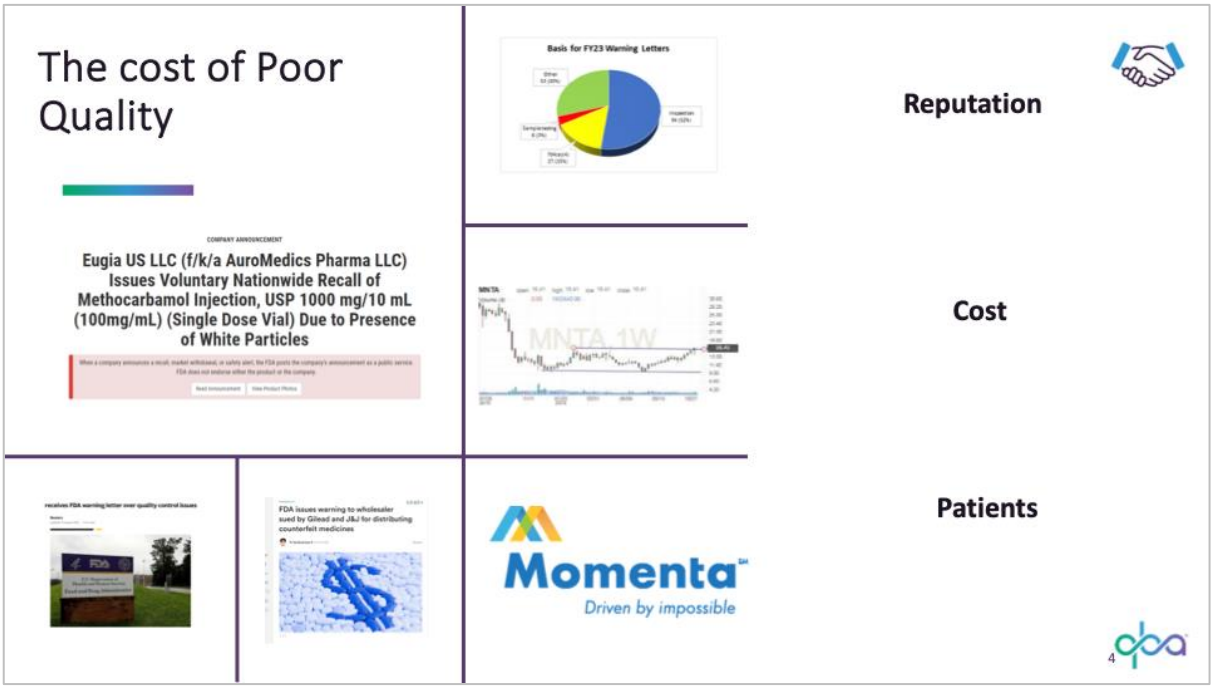

Figure 1 The cost of Poor Quality

Reputation: You can find multiple articles out there for different companies whose reputation is impacted by the cost of poor quality, whether it be a CRL, a recall, or a reject – so nobody wants that in their company.

And lastly, **patients**: no one wants to recall a product, and like Maureen said, we work in rare diseases, so we cannot afford to have any recalls, but it is not something you want to do. There is a huge impact on the cost to patients, but also on patient safety – depending on the recall. So, it is not a place that any company would want to be.

The Value of Quality

Under the same headings, the value of quality.

Figure 2 The value of Quality

Cost: This is Merck's stock price after they got an approval for one of their drugs a couple of years ago. It has a massive impact on the costs – sales, good quality, more product, more approvals, timely approvals. It can only be a good thing.

Reputation: A fantastic one. We get good quality and we have expedited validations and submissions, good inspections, and approval of a drug – it is all good news for companies. So it is great for companies and great for your reputation – also your reputation with your health authority. It makes for smoother inspections when you have a good partnership with your health authority and they trust you when they come around.

And lastly, again, it is **patients**. So, we are a very patient-centric organization, and good product quality, is just absolutely critical. The electricity comment we had earlier, it is true. It is assumed it will be there. Maureen mentioned that the patient's father and mother – as we heard a few times, are assuming the product is going to be there, and they are also assuming that it is good quality. So that is really, really critical for patients.

Using a Quality Management System for Investment in Quality

So, how do we, as quality business leaders, influence our organization to invest in and improve quality? Again, we speak in dollars. My interpretation of this is to use your quality management system.

So, this is a **typical QMS** that everyone has. This is our little house of QMS. We have our audit and inspection at the very top. They oversee everything we do and make sure it is compliant. We will have our inspections obviously for our regulatory submissions.

We have that oversight, that really important **senior-level oversight**. We have the QMR (quality management review), notifications to management of any significant events, and the 'quality council' for discussion of significant trends and any issues.

And then we have our **core processes** in the house:

- recalls
- quality risk management
- training
- computer system validation
- CAPAs and deviations
- change controls
- product complaints
- supplier quality, and
- document management.

They are all core systems for day-to-day manufacturing and release, etc.

And then we have **foundational documents,** which for everyone might be different, but for me it is our quality policy, having a strong contamination control strategy, QC strategy and analytical lifecycle management, and a data integrity policy.

And surrounded by all of that is something that we have all talked about today, which is **quality culture**. Quality culture is so important. It is on the manifesto we talked about today. Twenty years ago, this was something that was at the heart of everything at Wyeth, Grange Castle, and Frank Hallinan brought it in, to say that quality is a priority. So quality culture is critical as part of the QMS.

Figure 3 House of QMS

Proactive Quality Management

Moving into more proactive quality management, and how can we drive it? Proactive quality management is something that, as an organization, and as quality leaders, we really need to embrace because it will help us, obviously, move the dial from a quality management perspective.

But also, we can use it to work with our leaders in the organization to drive value for quality and investment. So there are four stages to the quality management system. There is:

- collapse

- reactive
- preventative, and
- systemic.

I don't know where you all sit today, but it depends on your management influences.

So, for a company, we will start with '**collapse**.' This is a company where there is massive complexity, huge growth, acquiring multiple companies and assets. They are not measuring it. They are not growing the quality organization at the same time.

Your **reactive** might be where there is some level of growth and variability, but they understand the complexity, and they grow the [quality] organization to support that. So they are reactive – not great, not a great place to be.

Preventative is where the variability is measured, so the company and the quality are growing at the same time and they are simplifying – as somebody said earlier about simplifying, streamlining, and modernizing from Janet. So that is a great one as well. They understand it and they will build on that.

And lastly, is where we would all like to be, and this is where quality is **systemic**. There is risk management, complexity is minimized, and that is where you want to be.

Industry Baseline

In the industry, the baseline is between reactive and proactive [preventative]. So, I think if you look at these different elements of a quality management system, you are going to find yourself in the middle of them both.

So, for culture, where we want to be in a proactive, or preventative, quality management system, is that you want your culture to be that everyone owns quality and that people are rewarded for being there and doing that. There are lots of examples of how you can do that.

For your product, we are trending to avoid failures. So you are looking at your CAPAs and really looking at CAPA effectiveness, and you are using AI to drive [understanding] what the problems are, really finding the problems and solving them – as opposed to just reacting to deviations and [problems] with the system.

Your QMS is suitable and consistently executed. In addition, you are using quality risk management, as Kevin talked about earlier on. You are using it proactively, not just for change management, but maybe for end-to-end quality risk management. So you are really understanding the risks in the totality of your processes.

And then, your QRM governance, just identifying the risks through periodic data review. You are not finding out about your risks through inspection or audit. You are finding them out yourself through full engagement and collaboration.

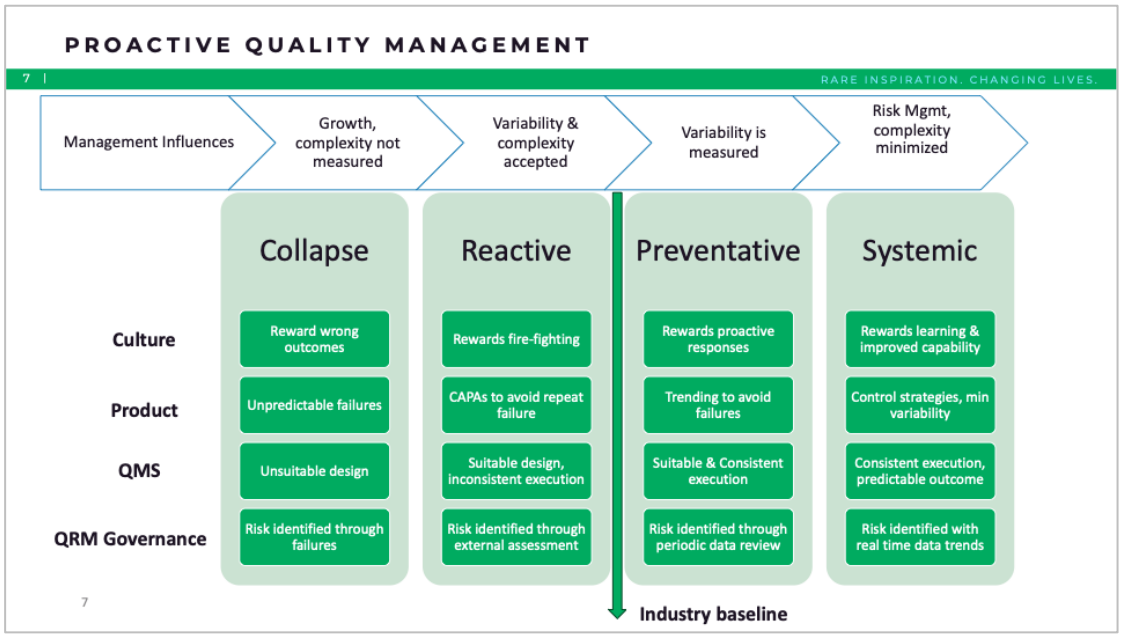

Figure 4 Proactive Quality Management

What Quality Can do for the Business

So, as quality business leaders, like we said, I think sometimes the only way to operate at the corporate level, is to talk about what we can do for the business.

How can we use proactive quality management? For me, it is a win-win. With proactive quality management you can improve your own quality management system, you can improve your inspection readiness, you can be in a much better place, and you will also get the investment and the value from your peers and partners.

So there are three areas where you can do that, and this is something that I would use a lot in budget planning to get a head count budget and the finances that I need for investment.

So, I will talk about proactive quality, bringing in:

- cost avoidance
- cost reduction, and then also
- knowledge management.

For a quality organization, QC testing, and understanding your deviations – the power of your data. You have so much information and data that you can use and help the business. So that is really important.

Cost Avoidance

For cost avoidance, from a proactive quality perspective, one thing that is really important, and one thing that I have been trying to do for the last 12 months, is to implement leading metrics.

So instead of lagging metrics, where we do our QMR, we come along and do our quarterly management review, and we look at the metrics from the previous quarter – so it is four months before

you are looking at something and you are looking at percent deviations closed, your CAPAs closed. Looking at these types of metrics is not effective and far too late.

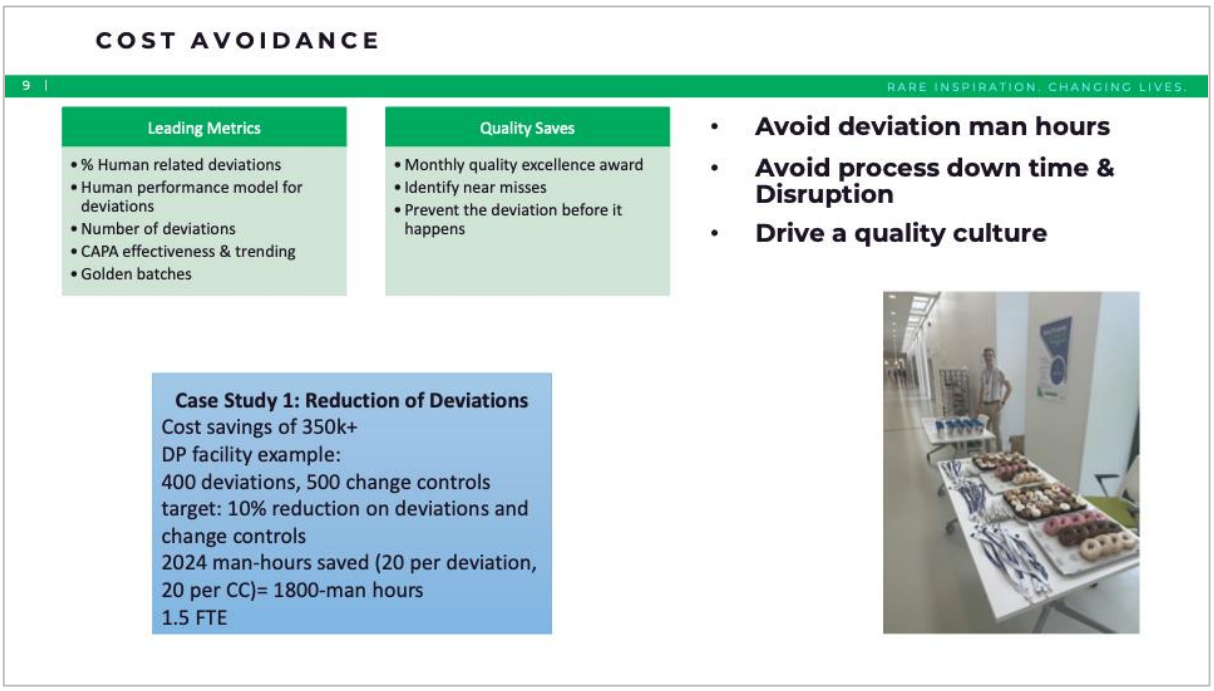

Figure 5 Proactive Quality through Cost Avoidance

Leading Metrics

With leading metrics, you are looking at trying to understand more about proactive quality management.

So, you are looking at putting in metrics for the percentage of **human-related deviations**. Month to month, what was the percentage of deviations caused by human error? What can we do to improve that? Can we implement a human performance element – techniques to really get to the root cause – because it is the process, not the human? So, put in a **human performance model**.

The **number of deviations** – and this is one I have struggled with before. Some of my industry peers believe in this as being a truly important leading metric, and I have been torn back and forth, but some believe if we are driving down the number of deviations, that is a really good leading metric. So, one I have put in is not just deviations, but also the rate of deviations that are occurring – a as manufacturing rates will go up or down.

And then **CAPA effectiveness and trending** – so really trending your CAPAs and using them with the likes of AI to look into your CAPAs and pull out stories, telling some stories about what is happening and trying to really come to a good root cause.

And then **golden batches** – probably a term we have all used, it is used quite a lot now. So, you are looking at those golden batches that were right the first time from end to end. And that, as part of the culture as well, to have a golden batch metric for your sites, just creates great visibility, something to get very excited about.

Quality Saves

Quality saves is another one, so from cost avoidance to quality saves by putting a program in place where you are looking at opportunities to prevent deviations and errors, and to recognize that and reward people. So that is something to look at.

I think it works really well. It is not a deviation, it is the simplest thing. A recent example I've seen was during a packaging operation, an operator noticed a torn label on a vial and paused manufacturing straight away. They searched the place and found the other half of the label, so they were able to attach it to the batch record, reconcile it there and then.

That would have been a massive deviation at the end trying to understand what happened, how it happened, and where it happened. And that is recognized by the person, celebrated, and they get rewarded for that.

So what we are trying to do with quality saves is prevent the deviation before it happens.

With these cost-avoiding measures, through leading metrics, reduction in deviations, and identification of near misses, you avoid the deviation man hours, process downtime, and disruption to your processes, and you are driving that quality culture.

Case Study on Reduction of Deviations

A typical example here of a quality save is in the drug product area. On average there may be about 400 deviations and 500 change controls in the year, and their target is to reduce the number of deviations and change controls by 10%.

We worked out that the man hours based on that is equivalent to 1.5 FTE. Now behind that metric is a lot of activity to really drive down those numbers and drive down those changes. But a lot of them are unnecessary. They are required for deviations. It is truly trying to identify the root cause and trying to remove the deviation.

For change control, what we have done before is look at the top occurring change controls and identified a process instead of the change control. So, we might have had the same change control for the same thing every single time and you are talking about 12-15 man hours. Instead, you put in a procedure and process in place. So stuff like that.

But just putting that target in play, that leading metric, it is good for quality, it is good for your inspections, because it will reduce those numbers of deviations you have to visit with the inspector, but from a finance perspective, it helps you drive value for quality. At your next budget cycle when you are looking for money or headcount, or investment to develop methods, or whatever it may be, you are saying we are going to save the bottom line.

Cost Reduction

Cost reduction, then. Ways to reduce cost include reduced testing, lean quality, and a network strategy. So trying to demonstrate the value of this is something we definitely do every year on budget.

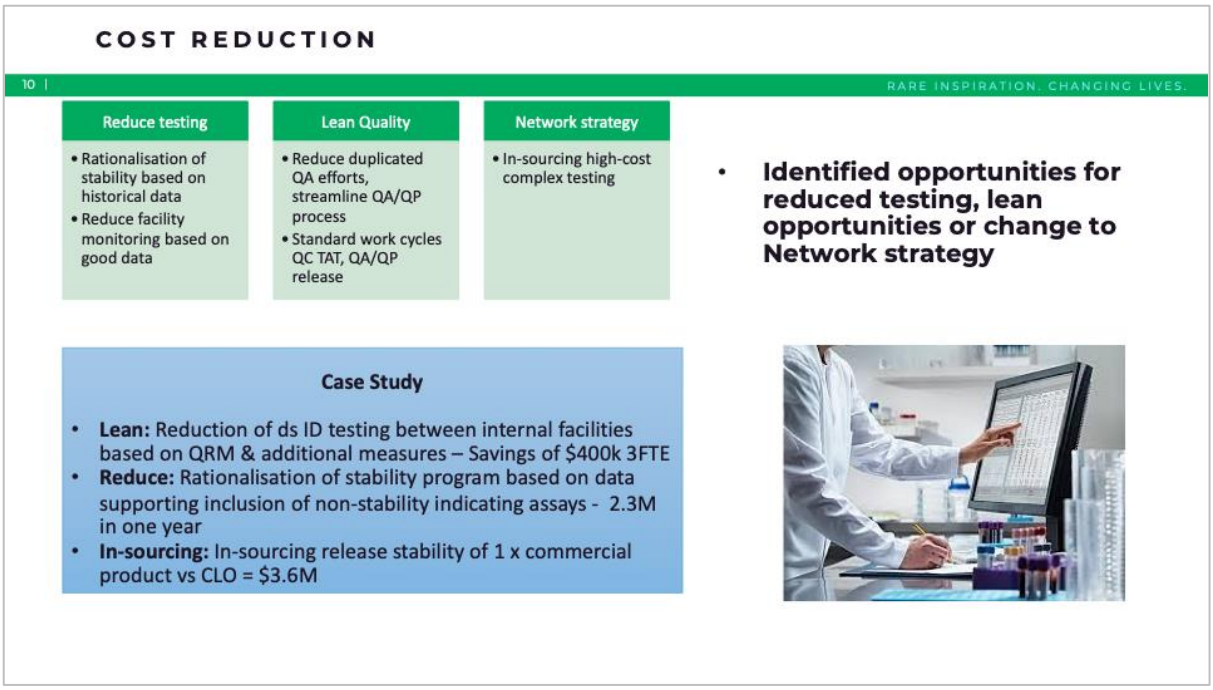

Figure 6 Proactive Quality through Cost Reduction

We will look at knowledge again, knowledge with data. So we rationalize our stability data. We look at our stability programs, we really test the data, and understand if there is anything we can do there. We reduce facility monitoring based on good historical data. Do we have enough data now to **reduce testing**? How much is that? How many samples, how many hours, how much money?

For **lean quality**, we remove duplicated efforts, so it is really looking at that value stream mapping of manufacturing quality or QP release – understanding where there is duplicated effort, streamlining it, and calculating those hours, and pulling that together as well.

And then obviously, with **lean labs**, this is massive. Testing is always the one thing that causes us the biggest headache from a corporate perspective as far as on-time release, up to getting batches to patients. So, the implementation of lean labs and reduction of QC testing turnaround time – that has massive financial savings and is something that you can pull together.

And then, network strategy, so looking at the high complexity, high-cost testing, and trying to get that in-house. A lot of the things that we tend to outsource are the ones that cause the biggest problems, like formal identifications, facility testing – stuff that you need quick, where you need to react fast. Look at your network in totality and [try to] pull it back in.

So, when you do all this cost reduction analysis and review here, the following budget cycle, you put all this together and you say, 'We are doing the following.' This can be massive when you do it all together.

But you are saying, I will save 2 million, but at the same time, I also want 1 million for stability, and I want this, and I want that – and all the things that we need to do, whether it is additional headcount, to put in the right quality compliant roles, inspection-readiness programs. That is what you want to put your money towards.

Case Study Examples

So, identify the opportunities. Here are a couple of examples of what people have done in the past.

For lean: There were two sites very close to each other. One made the drug substance, and the other made the drug product. It was not very far between the two. The drug substance went to the next site and had to go through full identity testing, which included Pep Map, which is the most painful assay in the world and takes about five days.

But it ultimately held off the release and the further processing of the drug product. So, through quality risk management and full end-to-end mapping, that was removed. That ended up saving 400,000 dollars because it took three full-time employees to do that testing every year.

Another one is to **reduce**. Rationalizing stability is one way. We really need to really look at stability and look at those non-stability-indicating assays. Why are we doing them? Why were they ever filed? If we went back in time, would we have taken them out?

So, look at that and try to rationalize it. Look at the data and refile. I know that is painful, but it is worth it to remove it. In one year alone, one example is saving 2.3 million dollars by reducing the stability [testing]. And that was approved, of course, by the way.

And then **in-sourcing**: So, when you look at your network for testing, the cost of external testing – although sometimes it is necessary – it is pretty big. So we look at our network strategy and look at our high-volume products, the ones that are really bigger value and important to patients, and we look at in-sourcing them. In the past, we have in-sourced some critical stability testing, saving 3.6 million dollars in one year.

So, it is pretty significant when you look at it holistically. And again, not that I would ever give this money back, but I use it to get something else.

Knowledge Management

And then, knowledge management. So again, as Anders said, in quality you have the opportunity to have access to all of the data. So much data:

- in-process
- release
- stability.

We know the process from working with operations.

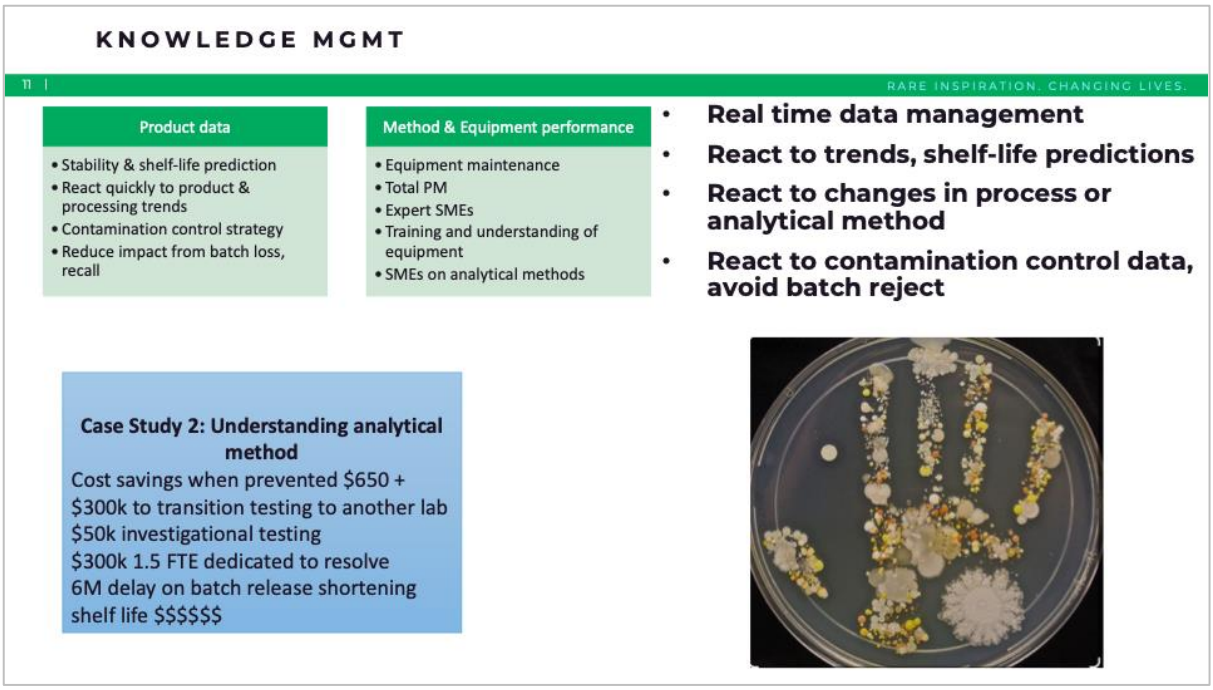

Figure 7 Proactive Quality through Knowledge Management

So the **product data** we have access to is stability and shelf life. We can react quickly to product and processing trends. We need to be really familiar with product lifecycle management and analytical lifecycle management. We need to be reacting to the data, amending and optimizing the methods, streamlining the process, and partnering with operations to do that.

Contamination control strategies are always the bane of everyone's life, but there is so much data for quality to recommend a change, to prevent contamination, and to prevent the loss of a drug substance batch. Batch loss has a significant financial cost.

There is so much data there that we can use to improve, identify heat maps in the process, and prevent batch loss, ultimately.

And **equipment**: equipment maintenance, total preventative maintenance – there are examples of some really complicated analytical equipment that have had new total preventative maintenance programs. The downtime has significantly reduced. It is just so critical because nobody really asks us how we are getting on in QC until something goes down. And when something goes down, we can't test it and we can't release the product, they are all over us. So that is critical.

And then **training** and understanding equipment and having SMEs as well on your analytical methods. So, invest in that. Understand. Know your data, know your methods, and know your processes.

Quality has that very real-time management. We have to react to trends and shelf-life predictions and react to changes in the processes and the analytical methods. Because an analytical method can shift over time, and if we are not all over that and it goes, again we are in a hole.

And then react to contamination control data – so really, avoiding that batch reject. Especially in the drug substance biotech world, we all know this. It is understanding your data, understanding where

your hot points are in your heat maps and really trying to prevent those batch losses because it is devastating when that happens.

Case Study on Understanding Analytical Methods

So, here is a new case study on understanding our analytical methods. Some time ago, there was an example of preventing a cost of over 650,000 dollars by investing some time in training for a specific, very complex assay. We sent people over to our sister site for the training. Luckily, we got it resolved. And when the method did cause us problems, and we could no longer test and release batches, we had the expertise internally, and we got it resolved super quick.

If we hadn't resolved it, our alternative would have been to transition to another lab, which would have cost $300,000 plus $50,000 for investigation testing, and we would have had to dedicate people to it. Also, because it was looking like it would have taken us months to resolve it, that would have shortened the shelf life as well – which is more money.

So, by investing in analytical capability at your site, you have prevented this cost. This case study alone has helped us drive investment in our analytical science and technology support at this site so that we can resolve those issues because this is the cost.

Concluding Comments

Ultimately, as quality business leaders, we need to talk in dollars in order to sit at the same table with our corporate leaders and convince them to invest in quality and that this is the right thing to do.

This is a win-win for us as quality leaders because we have more proactive quality management, we have better quality, better batch success, and more product for patients with fewer drug shortages.