Part 6: PANEL Questions and Answers Session

Panel members left to right: *Luke Kiernan, Paige Kane, Marty Lipa, Rick Friedman, Hal Baseman, John Lynch, Martine Nolan, Kevin O'Donnell*

Question/Topic 1

I would like to focus in the time we have left on the dynamics and tensions between the ***advancement of technology*** on the one hand, and ***regulatory science*** on the other hand, which are creating a regulatory *perfect storm* right now. Perhaps Regulatory Science Ireland can help solve some of this tension. Here's how I see it. We have the complexity of the processes and products that are dramatically increasing. We have accelerated review processes and shortened development times. We also have a relatively inflexible regulatory paradigm. It's aging, and it's relatively inflexible. So, there are tensions in this process. There is tension between the sophistication and potential of the science and the huge, vast potential of technology, Pharma 4.0 etc.

It is not essential to point out all of this, but there is tension in regulatory processes. What we need to do is to probe this a little. But the main tension has to do with change and the lack of flexibility around change, within countries themselves, and at a global level. So, if we start to probe the regulatory paradigm issue that advances in technology are racing ahead at this stage while regulatory science is less advanced.

Does anyone on the panel want to comment on this?

Responses from the Panel

Response 1:

We (in the FDA) have some Emergent Technology Teams (ETTs) and we have some PAT teams. CDER is very friendly to new technologies, with training in PAT, Isolators, closed systems. The fact is that we train in new technologies as we specialise more in the drug inspectorate. The Emergent Technology Team has a programme in place to give guidance, such as an e-mail address to send queries to, regarding new or innovative technologies. Even if we don't have ETT in place for the technology you are interested in, we still discuss things in our normal processes. FDA is ready for it, we have systems in place, we don't bite, we are human, we are happy to have a discussion with you, to give advice.

Response 2:

So, there are a couple of parts to my response. One is: I really think that what the previous panel member said does reflect reality. But, I think that to a large extent as an industry we have abdicated our responsibility for process control to the regulators. This is simply not fair. We are the experts in our processes and should know how to control them. When we either go to regulators and say what we would like to do, or accept recommendations from a regulator, It doesn't make good sense to abdicate that responsibility. To a certain extent: Shame on us! Regulations weren't set up to tell us how to control our processes. They were set up to judge if what we do is correct or not. I think that is a concept change that we need to do. So, as far as the regulators go, I think it would really help if there was a sharing of information as to what the criteria are by which the acceptability of technology is judged. What technologies out there have been accepted and what the reasons are. When I brought this up in the past the response was a lot of it is proprietary information, but that is just not true. Perhaps the information about the molecule you are using is proprietary, but for example, the use of different types of isolators is not really proprietary.

So, I was really intrigued by all the talk about knowledge transfer and knowledge management: that's all *intra*-company exchange of information. As an industry it would be pretty cool if we had *inter*-company exchanges of information. Individually we face challenges all the time in getting this to work, or that to work. But collectively we can probably solve any problem. So, as far as knowledge transfer and management are concerned, we would be pretty good if we could share more information.

Response 3:

Just to make another point. I do want to acknowledge that the regulatory affairs job is not an easy one. If you want to market in all the regions and all the countries concerned, the price you pay is to have to negotiate all those regulators.

The EU doesn't like it. The US doesn't like it. Japan doesn't like it, and we agree with industry and drove the ICH process to try to harmonise that, at least for these 3 regions. There are a lot of regions and countries left of course. But if you want a partner in Russia, Brazil, Turkey, etc, they well have a different system. I know that because I talk to a lot of people in industry all the time.

But you have chosen those markets, and if you choose to trade in these markets you are going to have to work it out with the regulators. For example, the US ended up agreeing with Japan that the supply chain system needed fixing and they harmonised it. In pursuing these regulators you have to apply the same philosophy. You have to say to them that the US and Japan realised they had to harmonise their supply chain system, and they did, you will have to work with the other regulators and apply the same pressure to bring it over the finish line.

Response 4:

There are parts of quality control that are inflexible. There are traditional approaches that are quite risk-averse. People can remember tribunals of enquiry and what politicians will ask if something goes wrong with a product. That does inform what we do. That said, there is scientific advice available for new processes at the European Medicines Agency. We can ask for advice there. We want to avoid the accusation of regulatory being too-close to the industry. There have been questions about that.

We (the HPRA) have an innovations office if anyone wants to talk to us about new technologies. It helps us to understand and it also helps us to advise around how this is likely to be regulated in the future. There are checks and balances there, but also there are ways to talk to the regulator, to know how your technologies will be considered in the future.

Moderator:

I think the message there is that there are channels for advice there, use them. Don't be afraid of them. One regulator has confirmed that 'they don't bite'

Question/Topic 2

A challenge for me, and I want to get the regulators' perspective on it!

I am a QRM person, so you can tell that I'm a big fan. I struggle with why the biopharmaceutical sector has more appetite for Lean Six Sigma than quality risk management. Why can we not use QRM to understand our processes, identify controls that we need to mitigate any risks in our processes? We don't believe that it adds value, or we can't actually convince our management, that it adds value. Yet we all use Lean Six Sigma champions and we have whole departments for it. But we don't get the same endorsement for Quality Risk Management. So, I invite responses from the panel about this.

Response 1:

I agree with what the questioner said. Industry will have to step up the game on risk management. Bring data and actually prove your point. We do ask the tough questions in the Agency.

On Lean Six Sigma, it's a good process. There are some excellent books on it, one from Professor Friedli, from St Gallen's University. There are great chapters in it. The good chapters point out that you can't lean out a process until it is stable, and what you lean out, really has to be risk. For example, if you have robust processes, can you eliminate inspections? It's not that you lean out inspections: it is that you don't have to rely on inspections. The inspection is valuable, but the point is you want to have to have as little waste as possible at the inspection.

Response 2:

Lean is about adding value. We don't really tend to measure the added value we get from QRM activities. We don't estimate using the risk ratings to get the risk reduction, and turn that into an argument about the increased quality assurance we have, and perhaps decreased use of valuable resources. This is hard to do when we don't have the tools to give us risk reduction measurements. We make risk reduction estimates all the time. With lean six sigma tools, and other approaches in lean, you do get more real-life measurements, which are occasionally cost measurements. Maybe this is one reason why you are not getting the benefit of the laborious work you do in QRM v's the other lean six sigma programmes mentioned. We are not there yet in terms of even remotely thinking about validating the risk assessment process, but we are making big decisions using risk assessment. This is one area we could consider working on.

Response 3:

A question to the audience as a follow up to the previous question.

If the collective regulators were to put an announcement out tomorrow that it is not necessary to use QRM at all, how many of your companies would stop using it?

Large show of hands

By answering in this way, do you mean a large number of companies would make decisions without considering the effect on patient safety and product quality. Probably not. That's the issue: we reflect the value of QRM to be something regulators want us to do, or to get in better standing with regulators – that devalues it. When we look at the success of six sigma and lean manufacturing which we are not doing because the regulators expect it, we are doing it for the shareholders.

Response 1:

The regulators considered QRM when they wrote the regulations. Every single GMP regulation is designed to mitigate a general risk in manufacturing.

'Thou shalt have procedures' to control your cleaning process, what is that doing? That is managing the risk that cleaning will be done in an uncontrolled way.

So, what is QRM all about?

It's simply understanding the specific risks, not the generic risks, embodied in the GMPs. That's all.

Response 2:

I used to do Six Sigma. The first step in Six Sigma is identifying the biggest risk you have in your processes and focusing on getting your SMEs just working on that. There is no point in trying to fix three things at once. *That right there is the problem I need to fix and I need to find the best way to fix it!* So, that is essentially Risk Management. It is risk identification the mitigation. Which further reinforces your point.

Question/Topic 3

My question is: are they not in parallel with each other? We really need to define understand our the processes. This is one of the core things with Lean and QRM. You are also developing metrics so that you can analysis how well you are doing them. Regardless of the driver, I think they both add a huge amount of value, and they complement each other very well, even if one is not a regulatory requirement.

Response 1:

I agree with you and I think they are very connected. We cannot do one without the other. But somehow it is Lean Six Sigma that comes before QRM. Leadership has more appetite for Six Sigma than for QRM. That is what I am struggling to understand. Why does the industry have more appetite for Lean Six Sigma than for QRM?

Moderator:

This in something close to my heart. Q10 is what motivated me to pursue doctoral studies focusing on protecting the patient and enhancing the outcomes by concentrating on the quality of the product. What I did was to bring the quality executives from three top pharmaceutical companies together with their Lean Six Sigma folks, to share the critical thinking with the Quality Executive. I like the term OpEx as it really is about building in excellence, which means you have a robust system, you have stable systems.

So, here's the headline: *What's good for the patient is good for the business.*

We regularly hear about OOT and OOS. OOS is there to protect the patient. OOT protects your business. If you are trending and monitoring, eventually you are going to use some of these industry 4.0 tools. If you really understand where your OOT is I guarantee you are protecting your business because the cost of poor quality is shocking. Nobody really counts it up. Nobody really looks at the annual accounts and says '*There's what it costs to fix everything we did not get right*'. Nobody counts it because it falls across so many different budgets. But it is something that we are trying to focus on at the moment, especially through PhD research on the cost of quality and on the business case for quality. The two actually go hand-in-hand because the business we in is delivering high quality products for the patient. So, we concede that there are tensions between systems. But there should not be. Manufacturers should pool all the resources of highly intelligent workforces to solve problems.

Question/Topic 5

This is a follow-on questions.

I do think Lean Six Sigma and QRM are a good match. But Lean Six Sigma did get hijacked by the OPEX people almost to the exclusion of a quality function. I think that in QRM there is a danger that the exciting profit controls we can see as the big-bang-for-your-buck and the problems that they might relieve, may have a role in undermining the function of the quality professional who is trying to develop PQS systems which are not always going to be based on process control, high investment control systems and big data. There is evidence of tacit functions in the operation as well.

So, my question is: What cautionary notes would you sound for the quality professional or quality director in an organisation to make sure that they can keep a hand on the rudder of PQS development?

Response 1:

I will answer this from a Knowledge Management perspective, not necessary for the whole PQS.

There has been a lot of recent talk around quality culture and when we look at knowledge management and QRM it's not so 'sexy' because it is a *Marathon and not a Sprint*. I would suggest, and be a little provocative here, that some of our senior managers thrive on results today, I fixed this problem today. There's not enough tolerance for making sure this problem does not happen. When I worked in quality operations I didn't want to do drama: that made my life harder. In essence we want to drama-proof our systems.

So what do we need to do then?

We need to understand our risks. We need to think thoughtfully about who are the people who have the knowledge? Are there ways we can convert the knowledge that is in people's heads and put it into the

business processes? We cannot get into the 'knowledge' heads' of these people. So, what happens when the Regulator show up for inspection? We identify the person with the knowledge and we pick up the phone.

Why do you have to do that?...

So, if our business processes were stronger and we really used the enablers , the tools of QRM and KM to manage the knowledge we have so that we have effective risk management. That does not mean merely filing in the data on a spread sheet. It means ensuring that you bring the best expertise to the table, having the right conversations. Then the knowledge should be reflected in the quality risk assessments.

Regarding QRM and KM, I think it was really insightful that it was put into Q10. But I don't quite understand how we use that to the best of our ability

That is just through my lens from a KM perspective.

Response 2:

I would just like to say something on two cautionary tales which I came across in the last 6 months or so. One cautionary tale is: it is going to get harder and harder to attract young talented individuals who are interested in technology. When I started my career, if you were interested in technologies you went to pharmaceuticals. Today, they don't want to go to pharmaceuticals. Nobody wants to get wet and dirty. They go to Silicon Valley. So, we have to be careful because if we talk about the great things that are out there we should keep this trend in mind.

The second cautionary tale is: I attended a talk some months ago where the discussions were about lack of improvements in the industry and about it being so stagnant.

We have regulatory issues. We have technological issues etc. Someone came up to me after the meeting and said, 'You know the way we are going to change things is to watch how companies like Amazon and Google are coming into our space. When they do this they are not going to put up with this stuff'.

Just some thoughts.

Question/Topic 6

Just in relation to quality culture, have any of the regulators seen the pharmaceutical companies embrace a quality culture? Have they seen any of the companies change their programmes? What might be used as a measurement of quality culture?

Response 1:

I don't do very many direct inspections now, but regarding measuring a quality culture, I suppose we could

look to senior management and how they focus attention on quality assurance, quality risk management and so on at the opening of inspection meetings. But we often during the inspection find that management commitment does not necessarily follow through. Sometimes quality processes are not quite in control, and there can be 'muddling through' with batches. This is not true for every case by any means. But, senior management does set the tone. If it is clear that senior management really won't tolerate sloppy practise in any organisation it is carried through in us finding very few issues. If there is a good quality culture at management level we see good product quality, fewer deviations, few complaints coming back. You can see a quality culture coming right through from the top of the organisation. In the European GMPs there is a huge emphasis on the role of senior management. Throughout the industry we believe that a quality management culture is really important. We put huge emphasis on the importance of the Qualified Person. That person is ultimately responsible for the release of a batch. If QPs are in a company where the quality culture is not quite right they will be under massive pressure. If they are not supported by senior management then, no matter how good they are, or how committed people are, there will be pieces of the quality jig-saw that don't fit properly.

Response 2:

A few things I would like to add to that with regard to Quality Culture, and in particular to key up the points of the previous speaker. Quality culture can be seen through things like: your cycle time, your on-time batch rate, your equipment capability and replacement of aging equipment, Capital investment in Manufacturing as an ongoing yearly expenditure, Supplier Management Programmes, Attentive Management of the supply chain, Taking ownership of supplier problems, Leadership visibility on the production floor showing their support, CpK measurements. These are leading indicators of Quality Culture, some are subjective, and not measurable, but some are tangible, such as checking your CpK or CAPA effectiveness.

Response 3:

With regard to quality culture, I would say that we have a very good 'compliance' culture. We sometimes do not distinguish between quality and compliance, especially if we meet all the tick-boxes. While we have a very good compliance culture we also need to ask why we are doing things to be compliant. We could ask if these things are the only things we could do. If there are other ways of doing things we should look at systems change. But we do tend to be very compliant in our behaviours.

Moderator:

Just following up that point. So, if we need to make the change from a 'compliance' to a 'quality' culture how do we do it? If we are looking at quality of final product we may need to go to 120 countries to ask them to make that change. Does that weigh in somehow?

Response 1:

Absolutely! This is one of the big challenges. It's a problem if we say we are not going to make changes to improve quality because it is too much of a regulatory burden. That is a problem. That's not right. How we fix it I don't know, but we need to do something.

While pharma in Ireland could be selling into 60, 70 or 80 different markets, the complexity gets bigger and bigger. We could get a change approved for one market in six months, but it could take up to three years to get approval in another. Basically then, we are running with slightly different products though all are compliant with local regulatory authorities. How do we manage our products between new and older versions? That is a real issue for us.

Response 2:

As long as we are still afraid of a high risk or red colour, or potential red colour, as long as we do not do things because we believe we have no money or resources to get things right first time. But we have a lot of money and multiple resources to do things over and over again. Then we do not have a good, mature quality culture. I think this is from benchmarking that still exists in some of our companies.

Moderator:

Could I add a note to that Please?

From being Chair of the ISPE cultural excellence team – we purposely called it 'cultural excellence' rather than 'quality culture' so that we might de-silo our businesses - not just to enable better knowledge management but because quality is actually everybody's business. So, once we can de-silo those businesses it is much easier to have an effective culture where there is no 'them' and 'us' with sets of checklists.

I would like here to comment on PDA where there is a fantastic assessment tool around quality culture. PDA and ISPE are working together for the first time on developing a 'root cause' guide.

So, there are tools out there. It does not really matter how many SOPs you have , how much training you have got, if culture is not healthy, you will not have a good product. So, think about investing in that team.

My last point is that achieving a quality culture is really difficult. But, after years of considering this, I came to the conclusion that it is all about behaviours. We should focus on behaviours and identify behaviours that contribute to good outcomes for your patient and your business. You focus on desired behaviours, and then reinforce these. You also identify behaviours that don't get the right outcomes first time and you eliminate them. If you start introducing change by means of behaviours it is much easier for people to digest that.