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Working Towards a Global Quality Dossier – Quality Leaders Turning Concept into Possibility

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First of all, good morning, everybody. Anders has asked me to speak about some work that is happening at the international level in terms of collaboration on post-approval assessments. I will come back to that in moment. But Anders, if you will forgive me, I think in view of the nature of the summit meeting this morning and the focus on two topics that are really close to my own heart – quality and leadership – I want to first share a few reflections on my own journey.

Quality Leadership in Ireland

As you heard in my introduction, I am the head of the Irish regulatory agency [HPRA]. And something I have always been very conscious about since stepping into the role is that – relative to other agency heads across the network of agencies in Europe and even on a global scale – most tend to have a clinical or a medical background. I have a quality background, and I have always felt that that was different.

In terms of my early career years, I worked in industry. I worked as a formulation development scientist, particularly focusing on GMP compliance. When I moved into the agency and during the 15 years in which I built my career, I worked in the quality area. I was a GMP inspector for a while, and then I also managed a team within our agency that is focused on the approval of CMC assessments.

I have always felt that quality was integral to my leadership journey because, at the end of the day, quality is a principle. It is about consistency and focusing on doing the right thing, setting a culture of excellence and innovation.

But also, I think, for quality leaders, one thing you really have to be good at is building relationships, because it is often about convincing and getting buy-in from others, particularly where you have to get a commitment for spend, and often you will face resistance. So I think they are all key tenets of leadership when you look at them.

Manufacturing Industry in Ireland

Also, in a meeting like this, and I know it has been mentioned in some of the introductions, you do have to reflect on the success of the manufacturing industry in Ireland. Everybody is very familiar with the statistics, but for such a small country, it is so impressive.

I will not go into all of them, but when you put this in context and think that between both pharma and medtech, by value we are one of the fifth largest global exporters, which is impressive. In terms of medtech, we are the second largest exporter of medtech products in Europe.

Both sectors employ collectively almost 70,000 between them and another 25,000 indirectly. You have to put that into the context that for a country like Ireland, we do not have that indigenous history of manufacturing, which actually for some countries goes back to the 1600s. It only began for Ireland in the 1960s.

We have had a rapid trajectory in bringing this to global significance. So there is something very special about that, and it really is an outcome of multiple factors:

- The strong R&D base that we have amongst the wider R&D sector in Ireland;
- The talent pool;
- I also think the open business culture that we have here has played a part and the excellent work of the industry associations.
- It has also had a huge government backing over the years, when we look at the excellent work that was done by the IDA [Industrial Development Agency] and EI [Enterprise Ireland].
- Regulation and strong regulation overseen by the HPRA has also played its part.

It really is what I would call a collective leadership. It is not just about individuals, or individual companies doing individual things – that is part of it. But it is a collective leadership, a collective vision for the sector.

So I think we can be really confident of our ability to lead in quality. And I do think that for the establishment and the concept of a network for quality leaders, Ireland is a very good home for it. I know I am a little bit biased, but I do believe that.

And now it is probably time to come back to what Anders actually wanted me to speak to you about today. But I think Ireland's position in terms of the global industry is a very good segue into that.

The International Coalition of Medicines Regulatory Authorities

I think for me when you take a step back and look at the intensive globalization of the pharma and the medtech industry, I have always really believed that that calls from us as regulators to really put concerted effort into working harder at bringing about more globalized approaches, pushing towards the convergence of approach, reliance, and partnership.

And I have always really felt that when you look at the array of regulatory activities that we have to focus on, it has to be easier in quality than it is in other areas because quality is a universal principle.

What I want to speak about is an initiative that is happening under the International Coalition of Medicines Regulatory Agencies focusing on post-approval changes and forging new pathways forward.

I know that the title of my talk refers to a 'global quality dossier,' but I do not want to get anybody's hopes up too soon. We still have a way to go in terms of reaching that point. But the foundations that are being put in place – and I will speak more about that in a second – are really opening up the mechanisms through which that can be achieved. It definitely is becoming a lot more possible now than it has been in the past.

The other thing that I am conscious of for some of you that are in the audience today, is that you may not know who the International Coalition of Medicines Regulatory Agencies are. So it is important that I provide a bit of context about that before I move forward.

Background

As its name suggests, it is a voluntary collaboration of leaders of agencies across all the global regions. All the major regulators are there, and at this point, the coalition is 10 years old. There are 40 participants in it.

I am also conscious this morning in speaking to you that I am standing on the shoulders of giants in the subject of ICMRA as well, because of US FDA and Janet [Woodcock], but also Pat O'Mahony, our former Chief Executive, who were absolutely instrumental in the establishment of ICMRA.

As I have said, it has existed formally for 10 years and the HPRA has been a very active participant over the decade of its tenure. It is going into its eleventh year now, and we have been members of its executive committee throughout. We have also held the role of vice chair, so we are very committed to its work and our involvement in that too.

Pharmaceutical Quality Knowledge Management System

The initiative under ICMRA that I want to speak about is called the Pharmaceutical Quality Knowledge Management System [PQKMS] project. I know Anders spoke about this from an industry perspective, and the 'One Voice of Quality.' It is amazing because it is almost a mirror image.

The vision for the project came from an FDA reflection paper. And again, Janet, I know it was part of your own handiwork involved in doing this.

What it set out was a proposition for industry in the context of post-approval changes to make one single submission to regulators globally. From the regulatory viewpoint, there would be a coordinated assessment of the post-approval changes – and these are all quality changes – and then a single outcome applicable across all of the regions.

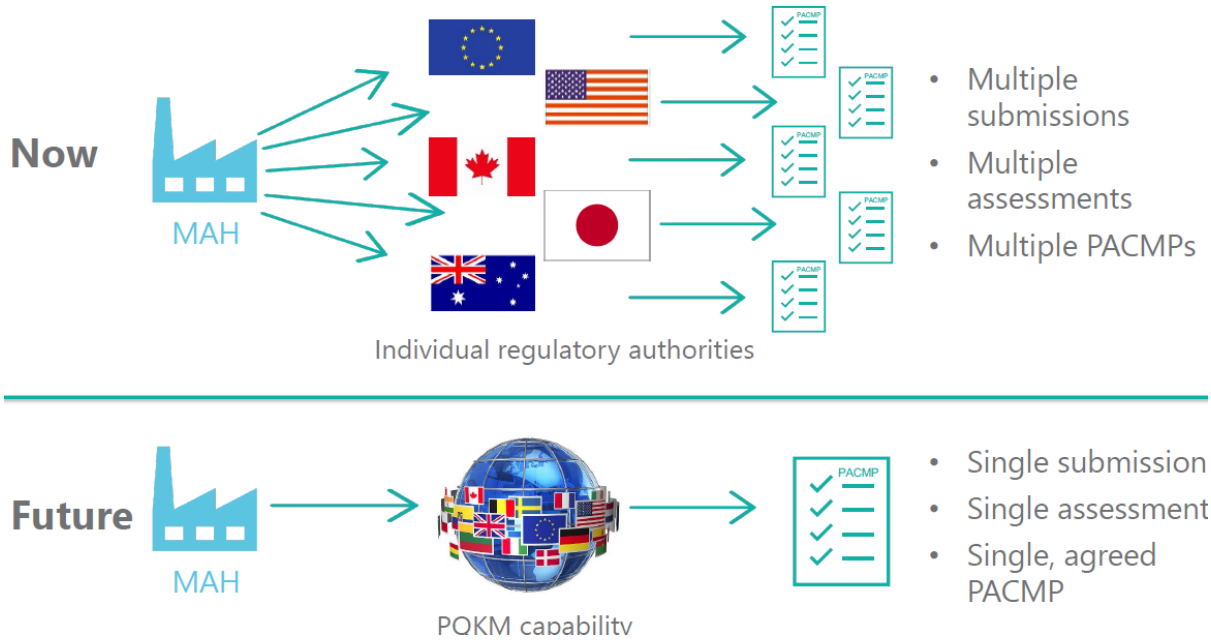

Figure 1 ICMRA Vision for a global PQKM capability

So immediately when you look at that, you think 'that makes perfect sense,' which it absolutely does. Things that come to mind include that it saves money and reduces complexity. But what it really does – and this is where the real beauty of this proposal comes into its own – is it actually introduces a different capability, to rapidly increase manufacturing capacity to address a variety of issues.

If you think about it, we have just come out of a major public health emergency, and this was a mechanism we used during the pandemic. But it also has a role in addressing shortages as well. It can be used to address unmet needs, and there are a whole range of issues that it can be plugged into.

So when I first saw the FDA reflection paper, given my own belief in quality, I immediately thought 'yes, this absolutely has to work.' The project was established in 2019 and I readily agreed to co-lead it with Theresa Mullin from the FDA.

Building Capability

The project is really focusing on taking this concept and building the capability among global regulators to actually deliver and achieve this.

The capability is split into two areas:

- The first is around the **collaborative assessment and inspection processes –** working on getting those established and defining them.
- But it is also about the **infrastructure** – both the digital and the data infrastructure that is really needed to support this. So, a repository for the receipt and storage of quality information that can be shared among global regulators relating to both products and facilities – but also the standardized and structured data elements, the standardized quality submissions, to be used by regulators across the regions to support different forms of regulatory decision-making.

In terms of the project, approximately half of ICMRA's 40 members are involved in this project. So there is a very high level of interest, which also speaks to the strategic importance of it.

Working in Partnership

One thing we knew in trying to get the project up and running was that ICMRA could not deliver this and could not deliver the infrastructure on its own because ICMRA itself is non-operational, with its focus being the provision of strategic leadership.

We really needed to onboard a partnership of expert international regulatory organizations – ICH, the Pharmaceutical Inspection Co-operation Scheme [PIC/S], and also the International Pharmaceutical Regulators Programme [IPRP] – because they would ultimately be the groups that would be needed to deliver the infrastructure components.

They are members of the project and very much involved in the working groups. As you can imagine, in terms of the coordination between ICMRA and all of those groups, the planning is incredibly important here. And something that I think we have managed to do incredibly well is to rely on the planning of the existing work programs of those organizations.

There are many examples of initiatives that are coming into the work plans here as well. You are probably familiar with them from an **ICH** viewpoint, including the M4Q revision looking at the revision of the Module 2 and 3 elements of the CTD, and also the work that ICH is doing on structured product quality submissions and the associated data models.

From a **PIC/S** viewpoint, it has a very strong focus on the harmonization of approaches for inspections. It has been working on training in this area and the approach to quality risk management. It is also looking at standardizing structured elements of inspection reports to make that information electronically transferable across the regions.

IPRP has a range of pharmaceutical assessment tools they are working on revising. Some really important work they are doing is looking at how to stimulate and converge expectations between regulatory agencies for post-approval changes, which is so important in terms of the collaborative assessment pilots.

Collaborative Pilot Studies

But I think that probably the piece that is the most exciting development under the project is the work that has happened in operationalizing the collaborative assessments and the collaborative inspections. This has been done through a series of pilots.

The pilots were launched just over two years ago and I think they have been incredibly successful in that period of time.

Assessment Pilot

The first is a collaborative assessment pilot, which is looking at collaboration among global regulators on the assessment of post-approval change management protocols, with the aim of facilitating alignment between regulators, and also applicants, on the implementation of future CMC changes.

When that pilot was launched two years ago, the intention initially was to use three test cases within the pilot. But there were a lot of applications and an awful lot of interest. So that was extended, and five applications were accepted under the program. Four have been approved over the previous two years, and the fifth is pending. In fact the approval should be due this week.

In relation to that, just to say about the nature of the products that were involved: This is a project that is focusing on post-approval change management for high-impact products that have a large public health value. There were two monoclonal antibodies, two small drug molecules, and an antibody-drug conjugate involved. The kind of changes were the introduction of new manufacturing sites, new QC test sites, container closure modifications, and also changes to manufacturing and QC testing processes.

In relation to the procedure itself, we have been working on finessing that and trying out different things. A 120-day timetable was agreed for the assessments, which aligned with the timetables from both the EMA side and the FDA side. We have found that that timetable is sufficient.

They are more burdensome assessments from a regulatory viewpoint – there is no point saying they are not. They entail much more collaboration, but that will improve, and that is what the experience is about.

With the 120-day timetable, it has been possible to manage the review of the applications, the follow-up with the companies, the review of the follow-up, and the information from that, all within the timetable.

I think probably the two most impressive outcomes from it are that among the regulators participating – one leading on the assessment with all of the others involved as participating authorities – are:

- The **achievement of a single list of questions** and a single list of requests for additional information. There have been some regional-specific questions, but again, they were to do with the requirements of those regions, and they have not had an impact on the timetable, and
- The almost **same-day outcome of the assessment** approvals across all of the various regions.

As we have completed each of those assessments, we are really keen to learn from the experience so that we can continue to improve. So, we have evaluated each of the experiences from both the regulatory viewpoint and an industry viewpoint. I think, overwhelmingly, everybody found the experience very positive. I know from the industry viewpoint that the synchronization of the approvals has been so valuable.

Hybrid Inspection Pilot

The second of the pilots is in relation to a collaborative hybrid inspection pilot. The hint is in the name. It is hybrid in that it involves both an on-site element and a remote element. One agency in a region takes the lead, and typically, the lead is on-site, and they are the regulator for that country or region.

A lot of the work has been done in terms of the coordination across multiple agencies participating in the inspection team, to make sure that the process is streamlined.

I can imagine, from an industry viewpoint, a whole host of regulators all participating in one inspection at one time – it is not always the most attractive proposition to be faced with. A lot has been done to make sure that the process is managed, running well, and is streamlined in terms of the focus of the inspection and the areas of questioning that are covered within it.

Under this pilot, three collaborative inspections have been carried out. Two are complete, and one will be completed in the coming month. Again, we have been analyzing the outcome and the experience at all stages.

Something that we did in the process of the pilots as well is that the implementation group for this pilot put in place an expectation guide for industry. I think that really helped clarify to industry how these inspections would be run and explained relevant practical considerations a lot more.

Future Directions

After the pilot programs are completed, the intention is to write up a full report on both pilots, with the aim that that will be published this year.

Both implementation groups are now thinking, 'What's next? What can we learn from these? How do we extend these pilot programs? How do we do more? How do we extend it to more types of applications?' There really is a strong appetite from a regulatory viewpoint to keep pushing this and to keep going further.

One of the reasons that I really like this project is because it is an example of innovation that is not actually about the introduction of anything new or anything novel. It is about reducing complexity.

I know we have had many initiatives that are looking at collaborations on inspections and collaborations on assessments, but there are some differences about this that I think really sets it apart for success.

The first thing is that it is an agreement at both leadership and the expert level on a vision for what can be done here. This is the first international regulatory project of this nature that involves participation and collaboration between ICMRA, ICH, PIC/S, and IPRP. So it is a shared vision.

Also, the partnership with industry in this program has been hugely important. Industry has been involved at all stages in relation to the design of all of the pilots and giving us feedback in relation to the pilots.

Opportunity for Co-Design of Pathways

But there really is an opportunity here for the co-design of future pathways. So, one of my calls this morning for you is to really come on board with this project, get behind it, and push it.

We have had challenges in terms of the collaborative assessments and inspections, in terms of quality leaders in the organizations getting the buy-in at the CEO level to participate in those inspections.

I think from our side, we have really worked to reassure everybody involved that this is done with the right intention, completely. It is not about increasing burden. It is actually about reducing complexity. So I think the proposition of selling it within your companies is really important.

That opportunity for co-design: I cannot emphasize enough how much we do need that because it is about the future and future possibility.

I also really like the fact that it has potentially a huge public health impact in terms of that ramp-up of capacity to increase manufacturing.

Finally, I think it is scalable. When we are talking about post-approval change management protocols, there is an awful lot that can be done once we get this set up, we get the processes established, and we get the infrastructure. And we honestly are really getting there.

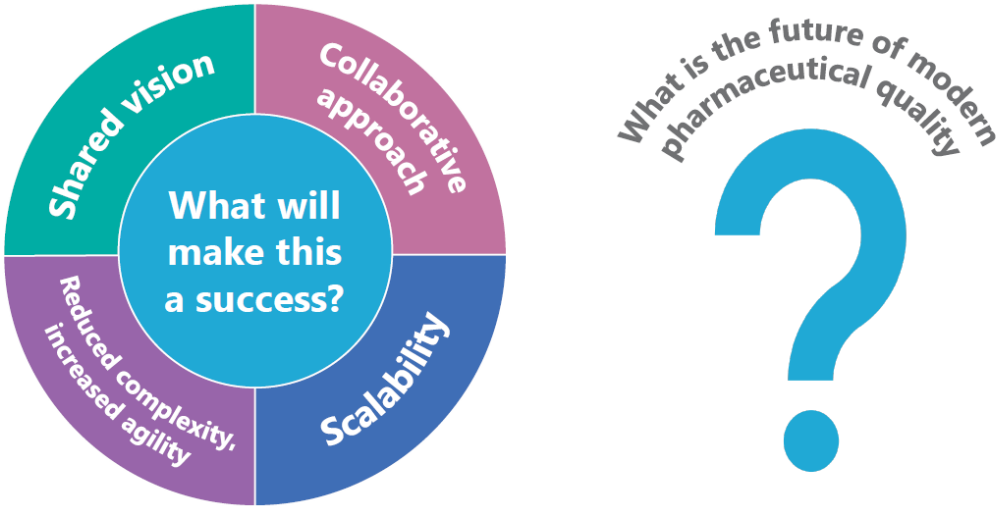

Figure 2 What Comes Next?

Take Home Messages

There is always a take-home message on a day like this. Something I would like to say this morning concerns modern pharmaceutical quality and what it really takes. It is definitely a lot more than just complying with regulatory requirements and complying with regulatory guidelines.

I know in all the years that I have worked with the HPRA – and that is many – we all too often see that companies just focus on that goal of getting through the inspection or getting through the product approval, rather than looking at systematic issues and processes as a whole, looking at the problems, and actually fixing them. That is the kind of approach that really drives excellence in quality management and quality risk management.

Even if we look at ICH Q9 as a case in point – and I know Kevin [O'Donnell] will speak about that later today – ICH Q9 has been in place for almost 20 years now. Industry has used and applied quality risk management principles over the entire 20 years, yet we are still seeing high numbers of quality defects and serious quality defects.

So there is something in the application of quality risk management principles by industry that is not working. That is a question for quality leaders: 'Why is that the case? And how do we actually work to address that?'

Regulatory Evolution

Also, in the context of modern pharmaceutical quality, we cannot stand still as regulators. We have to continue to evolve, and we absolutely know that. There have been many initiatives. The GMPs have gone through several iterations of revisions, ICH Q12 and Q13 recent initiatives, the revision of Q9, the work of PIC/S, and there are many more examples.

But we also know, when we speak about data, and science, and regulatory science – that for us is really important too, because that is how we will become much more risk-focused. And actually, data, and access to data, is how we also coordinate activities in the quality area of both product assessments and inspections.

I do think the infrastructure on this PQKM project is really giving us the knowledge management capability to drive that forward.

Finally, I know Janet, that you retired from the FDA at the end of January. I was very struck by something you said in an interview with RAPS when you were leaving, when you were asked, 'What is the advice that you would give to regulatory affairs personnel in the evolving environment?'

I thought it was such an intuitive answer: 'Look at what the problems are and try to figure out what the solutions are. Simplify, streamline, and modernize. Use the best technology and use the best processes.'

That is really how you drive excellence in terms of quality management and quality risk management. For quality leaders, when you have to convince the CEO of the business proposition that quality is, not the cost center, that is the way to do it.