PFIZER’S ROGER NOSAL ON PHARMA AT THE CROSSROADS OF A NEW QUALITY PARADIGM

At the ISPE/FDA/PQRI conference in June, Pfizer VP and Global CMC Head Roger Nosal explained how the pharmaceutical industry is at “the crossroads of a new quality paradigm,” reflecting the impact of “transformative” innovation, development and review acceleration, and global regulatory harmonization. Nosal began with a review of the pharmaceutical landscape and its achievements. The innovation discussion included references to precision medicine, continuous manufacturing, hybrid integrated manufacturing, and multi-attribute monitoring. He then reviewed the benefits and challenges for CMC of acceleration, finishing with the progress industry and regulators have made, and the shortfalls, in moving down the global harmonization pathway.

At the forum before this, at my table, we talked about failure, [and] I mentioned this at the table: Failure is really important. If you don’t try, you won’t fail, but you also won’t succeed. As a good colleague of mine that I work with has often said, you have to play to win. You have to play to do the things that you need to do.

What I am going to talk about today in this keynote involves playing to win in terms of collaboration. I am going to look at this in terms of three, what I will call ‘crossroads’ – innovation, acceleration and regulatory harmonization – and what we can learn from them in what we should be doing moving forward.

This is the disclaimer, and this is the abstract. The real key to the abstract is that we are facing in the industry some fairly significant pressures. And those pressures – particularly acceleration, but also some pressures to try to innovate more – are causing us some grief in the regulatory arena.

I don’t mean this directed at the regulators themselves. This is not about necessarily barriers to doing regulatory work, although I will identify where I am seeing some discrepancies. It is the fact that in a global arena, there are so many differences about what the regulators want for us to be able to accomplish this. It actually creates quite a difficult situation.

The new global paradigm that I am going to try to describe involves connecting these items.

● First I am going to do a quick pharmaceutical landscape review.
● Then I am going to talk about some of the innovation that many of you are probably familiar with.
● I will talk a little bit about acceleration.
● And then I will talk about harmonization.

One underlying theme that I am going to try to connect you all with is that there is a need for collaboration across the globe – not only among industry, but with industry and regulators.

If we have learned anything from quality by design, we learned that being transparent and sharing knowledge is actually the biggest benefit to this industry to the extent that we can do it…. We did not progress anywhere until we started sharing some of the work we had done individually in our companies. And we did not get anywhere with regulators until that was very transparently shared with them and they shared with us. That is kind of the key to all we try to do.

Pharmaceutical Landscape

So to start the pharmaceutical landscape: I stole some slides from a presentation from PhRMA on what medicines can do with in our lives, and of course the patient is central to that.
First and foremost, medicines have significantly increased the chances of survival and quality of life. PhRMA has a lot of statistics, I know EFPIA has some statistics, and I am seeing some statistics from some universities [indicating that] people are living longer because of what we do. And the quality of life is much better. And I think we have to remember that as we do the work that we do. It is very important.

However, the costs have increased significantly – the costs to deliver these new innovative therapies. You think back 15 or 20 years, many companies were making ‘me-to’ drugs – drugs that were similar to other drugs on the market. We are not doing that as much anymore, at least not in the innovator space.

In the innovator space, even though we are competing as companies, we are trying to make sure that our drugs are a little bit different. Part of that is because of the etiology of patients, the genotypes…of patients are different. So some drugs behave a little bit differently, even though they are for the same indication.

And despite the cost, there are still some really impressive achievements for transporting the treatment of almost all the chronic diseases today. We are getting much closer, in some cases, to understanding diabetes, rheumatoid arthritis and cardiovascular disease than we have been in the past, which I think is a significant step forward.

**Vaccines:** Right now, the vaccines that we put out in the market, the ones that we use, are being distributed widely around the globe. WHO and the Gates foundation are helping us to do that. As a result, we are actually making a difference in lives of people who wouldn’t otherwise have the opportunity to benefit from them.

With respect to HIV and AIDs: One of the reasons I put this up is because there was a very strong push in this country, in the US, during that crisis in the late ‘80s and early ‘90s that actually propelled not only the FDA but industry to act. And they acted in such a way that they have been able to stem the tide on HIV – not only in this country, but globally.

Finally, **rare diseases** have become a focal point for many companies. Pfizer, my company, has been engaged in this through partnerships with a lot of smaller companies that have come up with interesting and innovative therapies for rare diseases.
The interesting thing about rare diseases though, is that they add a significant challenge to how we operate, because we typically do not manufacture significant quantities, since these diseases, by very definition, are rare. Therefore, there is a limited amount of drug that we are providing to these patients. In addition, we probably are accelerating these because they are for unmet medical needs that otherwise would go untouched. People would die or people would suffer.

Having put that landscape forward – which to me is somewhat positive even though the costs are high – I want to talk a little bit about the specifics related to innovation to start, and then I will talk a little bit more about acceleration and harmonization.

**Transformative Innovation**

This picture [is] meant to reflect how you might do things the old-fashioned way – manually, kind of focused on things that probably are not going to get you as far as you want, with a lot of potential error. We have to start moving innovatively to more automated systems. We have been saying this for a long time, but I think we are now on the verge of trying to get some of that automation out there.

What that means then is, with less human involvement in the manufacturing, we should reduce the risks of error. And we should end up with a more reliable and dependable manufacturing environment. That is really the goal of innovation.

Now, for those of you who work in large companies, or even if you don’t work in large companies, you know that pushing innovation in manufacturing is not the easiest thing to do. Because a lot of times manufacturers will say, ‘why do I want to do this? Everything is just fine. I am doing it fine. Keep turning the crank.’ I really don’t think that that is fine.

So what are some of the transformative technologies? I have listed four major groupings here. There are others that I didn’t capture. This is not meant to be a complete laundry list. These are just some of things that have come to my mind in the past few months:

- Precision medicine
- improved manufacturing, including things like continuous manufacturing
• performance-based control strategy – I think that is a huge area that we can improve and learn from. Clinically relevant specifications is a very hot topic these days and is one I think we need to tackle in a collaborative fashion, and using some sort of performance-based control strategy is really key to delivering them

• and then, of course, patient focus and compliance – how do we make the medicines that we produce much more amenable to patients for administration.

And if we do that, I would argue that the uncertainty that exists in some of the innovative space can be addressed and that we could end up showing robustness, consistency, reliability and sustainability for our products.

Transformative Technologies

1. Precision Medicine
   - Cell & Gene Therapies
   - Nano-Robots

2. Improved Manufacturing
   - Continuous Manufacturing
   - Mammalian Expression Intensification
     - Bioreactor Productivity
     - Condensed Harvest
     - Low pH Virus Inactivation
     - Cell Culture Profusion
   - Purification Sequencing
   - Packaging Platforms
     - Aseptic Glass Vials
     - Bottle Resins

3. Performance-Based Control Strategy
   - Clinically Predictive Modelling

4. Patient Focus & Compliance
   - Spray Dried Coatings
   - Micro-particulates

But it all comes down to **partnerships**. None of us are going to be able to do it alone. I speak from the perspective of a large company that has literally hundreds of partnerships with others. The reason that we do is because we recognize that we need to work with other companies to make this work. We also need to work with the regulators to deliver on some of these things.

So I am going to talk a little bit more in the next few slides about some of these specific transformative technologies and where those partnerships can really become much more salient to all of us.

**Precision Medicine**

**Gene therapy medicinal products** [GTMP]: The reason I am putting this up here is because we are moving into this realm much more directly. Again, it is part of what I would I call a form of a precision medicine approach.

If you look at this in terms of the **delivery technology**, it is relatively novel. We are using vectors. Many of them are adeno-associated vectors. They are adenovirus vectors that can infect a cell and deliver what is essentially a genetic change that would actually have the human body do the work for us – almost like having a little manufacturing site within the human body.
The *infrastructure* for this is relatively old fashioned right now. We are using roller bottle technology, and I will show that in minute. But the interesting thing about it is that there is a tremendous amount of room for innovation that will get us closer to where we want to be and with much more…reliable approaches.

From a *clinical and regulatory* perspective, we are doing very small studies, and based on those initial small studies, we are actually determining how quickly we can commercialize. We have a very limited amount of data, which means that we aren’t going to always know what is going on with these products. We will have a fair degree of uncertainty as we go on into the commercial realm. So we need a little bit of latitude on how to operate and to understanding how we are going to manage it.

Here is an example of transformation that we are already talking about. We start out with lab scale culture roller bottles that we actually deliver the product from to the patients. It is a limited number of patients. In one case that Pfizer is working on right now, there are only 24 patients.

But we want transition to a much more platform-oriented technology, which is more of a contemporary, scalable process that we could use as a platform for a whole host of these particular products. It requires that innovative approach. It also requires a regulatory engagement on that approach jointly around the world.

So let me tell you what we have done as an example of where I do have some concerns. We have gone to the EMA, and we have had a very nice discussion with the EMA about how to move forward with that while we are in development. We have spoken to the FDA, and we have had some very good discussions with them. We have spoken to the PMDA in Japan – again, some very good discussions. We are going to ANVISA as well as to China.

The interesting thing when you compare the notes, everyone has a different set of criteria that they want us to live by. My [idea] is that we should get everyone in the room and let’s talk about it. Because this is life changing medication, and most of us are working on that right now. I am not talking about parallel reviews. That is kind of what we are already doing. I am talking about joint engagement. I would rather risk in the joint engagement the differences coming out in a meeting, than trying to do it individually. That takes too much effort and probably won’t get us where we need to be.
Just some of the [CMC] challenges, and I have already mentioned most of this, so I will not go into too much detail:

- We are going to have to determine criteria for manufacturing these products with a very limited data base and experiments.

- The clinical program is compressed. The number of trials is limited, the number of patients is limited. The data is again limited in terms of supporting it. So that means in some cases, you will not always know if you have a good cohort of patients because every patient is different. There is a tremendous amount of variability among patients, particularly in these cases in rare disease.

- We need, as I said, to align strategy across the regions because we can’t progress these without it.

**Continuous Manufacturing**

Continuous manufacturing has got an interesting history. I am going to talk a little about continuous manufacturing in the last decade. But, there was a presentation about a month ago by someone who I know pretty well. He was making a very keen observation that has kind of escaped me, and that is that we are actually going back in time when we do continuous manufacturing. We used to do continuous manufacturing in the ‘30s and ‘40s. Fermentation was a continuous manufacturing process. It wasn’t what it is now, which is more batch, which is a good thing. Hopefully we have learned that going to batch was not necessarily the way we want to go now.

But I can also tell you we have run into some glitches, particularly when we have done some manufacturing using continuous approaches, where the cost of maintaining the continuous manufacturing was too high for some companies to bear.

There are two examples here. I have just put up representative information of some things that Pfizer did in 2006. We had a dry and a wet granulation process – both were continuous manufacturing processes. We developed them. We actually had, in one case, the FDA come down and meet with us to see what we could do. It was fantastic. We had a great engagement with the FDA.

And then we went back to our manufacturers and said, ‘what do you think? FDA is telling us we can do this and we can do that.’ Our manufacturing guy said, ‘you know what? If every time we make certain calibrations for our analytic methods online, we have to submit that information, it is going to be too much of a burden for us.’
Recently we had the same discussion with some folks at EMA on continuous manufacturing. In fact, if you go back to quality by design, where we introduced real time release testing, one of the biggest issues that came up among the manufacturing folks was, ‘this is going to cost us more than it is going to save us, because we are going to be spending so much time in trying to reconfigure the calibration or our instruments and submitting those for approval that we are never going to get anything done.’ So that is an issue that we have to address.

The new continuous manufacturing that we have embarked on is a miniaturized version that I am showing here. There have been a number of presentations at ISPE and other venues on miniaturization of manufacturing process manufacturing PCMM.

The issue here now is that we actually collaborate with regulators, and particularly the FDA, to talk about where these issues are and what we need to do to address them.

So if you look at the regulatory criteria that becomes the hot buttons for this, it is: ● the definition of a batch ● lot traceability ● batch uniformity, and ● process upsets. If you can have a good strategy and program around those generally, regulators are reasonably comfortable that we can move forward. We have those conversations, and that is why we are moving forward.

But there are some global challenges, and these are challenges that we have heard from regulators in other places around the world. They go down the normal list of things that you would think you would have to deal with. Can you change the batch size? And sometimes that is something that is not particularly acceptable. In fact, in some Latin American countries, if you do that you are going to have to file almost a brand new submission, the process description.

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<th><strong>Continuous Manufacturing</strong></th>
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<tr>
<td><strong>Regulatory Criteria</strong></td>
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<tr>
<td>● Definition of a Batch</td>
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<tr>
<td>- Required to file a “batch size”</td>
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<td>- Characterize run time (hrs) vs. volume (# kgs)</td>
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<td>- Justify max run time w/data</td>
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<td>● Lot Traceability</td>
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<td>- Trace raw material pedigree</td>
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<td>● Batch Uniformity</td>
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<td>- On-line analytics critical to demonstrate batch consistency</td>
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<td>● Process Upsets</td>
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<td>- Demonstrate process perturbations are managed</td>
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<tr>
<td><strong>Potential Global Challenges</strong></td>
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<td>● Ability to change batch size?</td>
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<td>● APC vs. PAT Monitoring</td>
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<td>- NIR - # of batch &amp; scale to qualify model</td>
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<td>- Model Updates?</td>
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<td>● Lifecycle Raw Material Control</td>
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Whether or not you do adaptive process controls or PAT monitoring, again we have to figure out how we can make changes to those – to make sure the calibrations are correct, the algorithms are correct – without having a tremendous regulatory burden. Managing that is going to be critical.

And then all of these others actually apply to conventional processes as much as they do to continuous manufacturing. There are differences that you see around the world.
Hybrid Integrated Manufacturing

Hybrid integrated manufacturing is something that some companies are working out together to actually improve what I call continuous manufacturing and intensification of manufacturing in the bio space, for biologics.

I am not going to go into a lot of detail here, but one of the nice things about this is you can actually reduce the overall time, particularly hold times, which are an issue for biologics, down to almost minutes, rather than hours or days, because you are not segregating anything. You are just moving it through the system. At the end of the day, you have got the drug substance that you can use.

It relies very heavily on adaptive control-based manufacturing – meaning you can adjust things during the course of the manufacturing, because you have adaptive controls in place to provide you with the information to detect perturbations.

We have already estimated that we can reduce costs for [clinical trial materials] by 50-75%. That is significant for biologics. And for those of you who are operating in a biosimilar space, or a biologic space, that would be a huge boon to your business and the industry.

We also have demonstrated that we can reduce the time to get into first in human by about 40%, meaning all that extra work that we have typically done in the past, we can now consolidate and actually deliver products to the patients for initial evaluations. We can improve the clinical and commercial capacity well. And for a while, there was a capacity issue in the world with respect to monoclonal antibody manufacturers.

Multi-attribute Monitoring (MAM)

This is pretty cool stuff. This is multi-attribute monitoring on line – doesn’t have to be on line, but it frequently is. It is a way of identifying glycosylation, oxidation, deamidation, heterogeneity and other modifications and clips with much more precision and accuracy for biologics. And that is a tool that we have not had at our disposal. We are starting to implement this now.

What it does is take out the uncertainty that I talked about early on, which means that these become much more viable and can be leveraged in a way that can actually deliver medicines to patients much more quickly.
Acceleration

So acceleration: Most of us have been embarking on acceleration for a number of reasons – mostly because we have patients that need our drugs, and we have been able to work with the regulators to identify mechanisms for doing that.

But it does require significant change in the investment paradigm. The red line shows an accelerated paradigm, where we are doing some investments early on during the proof of concept. This is when we are getting through phase 1, phase 2, and we are starting to recognize that we have some mechanisms that can tell us that we have a clinical signal that is worth pursuing.

You can see the blue line, which is more of a base case that it is a little bit more graduated in investments, whereas in the red line there is truly a significant investment. When I talked about cost earlier, that is where a lot of the cost is going – that initial investment for these accelerated programs.

What this does for CMC is that it really puts us in awkward position, because we have to identify the risks without really knowing the problems. We don’t have as much experience. We also want to be able to integrate what we are doing for review and inspection, because they are going to come on top of each other. And we are not necessarily going to have a complete commercial program the way we would like – an optimized program – when we get commercial approval.

Our clinicians and our commercial business, they are just ecstatic about moving these things forward. To us, it is, ‘oh my gosh, how are we I going to do this?’ I have to credit Susan Burling for this. She came up with the slide a while back. And I have to say it is probably the best reflection of acceleration I have seen.

But there are huge benefits. And it important to recognize that those benefits can actually help us in the collaborative approach that we take….

I am also speaking about mutual recognition. If we can in the future push forward with joint and or mutual recognition approaches for global regulatory agreement, it is going to be a huge boon for us in the industry and for patients, because we are going to be able to deliver products faster to more patients, with less hassle, less delays.

I don’t show slides here on some of the concerns related to the delays. But just for everybody’s edification, and I think you already know this, one single process change that needs to be filed globally can take five to seven years to get approved. That is absurd. It should not be that way, and we should be able to find a way to fix that.
Now acceleration often comes with **simultaneity**. Most companies that I have been working with or working in, we would always prepare a filing for the US, Europe or Japan first, and we wouldn’t do them necessarily simultaneously. Sometimes we would file in the US and Europe simultaneously and sometime not. Japan was its own little entity because they have some specific criteria that are a bit different. We rarely file all three of those at the same time, or any of the others at the same time that we file the first one, because it is hard to manage.

We are seeing this more and more with accelerated and particularly with unmet medical need where patients around the world would benefit. When you add simultaneity to acceleration, you now magnify exponentially the amount of work that you have to do.

What I was hoping, and what I am still hoping for, but I think I am going to be retired or dead by the time it happens, is something related to mutual recognition.

I am seeing work sharing. In Asia, the ASEAN group is doing something called work sharing which is very successful, where you file your CPP and your new application to that group. They do a review, and then by mutual recognition the other ten countries that are in ASEAN approve it on top of the other approval. I have seen limited success there, because typically what has happened is more questions get asked, so you still have some work to do. But it is generally moving in the right direction. And I think we need to see more of this.

We have to recognize the difficulty of having to manage multiple approval cycles or approaches for some of these products if we are going to try to do simultaneity.

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**Regulatory Harmonization**

Regulatory Harmonization: By the way, I have ICH down here. I still think ICH is one of the most viable ways to try to get people together. I have been working with ICH on and off for the last 20-odd years. I would have to say that most of those, while they are difficult, and it is kind of like the United Nations getting together, we do actually deliver things that help move us in the right direction – to address some of the topics and issues in the right direction.

By the way, ISPE can play a big role in that and already has – in defining what the implementation and the alignment is across the industry for some of those ICH topics. I think that is one area that we have to get back to in earnest, because I think that it is really important for the industry.

**Regulatory Divergence – Global Trends**

But there are some **major divergences**, and I have identified some here, and I am only going to talk to a few of them. Even with ICH we have unpredictability. There are still countries that say, ‘yea, I accept ICH but.’ And then the but is, ‘well you need to do certain things well beyond what ICH would tell you. And even when you have [agreement] in some countries for some things, you still have other countries that say ‘I don’t agree.’

One of the interesting things that Bob Tribe shared [at the ISPE Europe Conference] in Barcelona is how many compendia there are. I did not know there were 49 compendia. I guess I didn’t know because in some countries locally, those compendia are separate. And they are not necessarily aligned – they are used as separate for the individual manufacturing in that country, not necessarily globally. But still if there are 49 separate compendia, that is 49 separate compendia you might have to adhere to for specification criteria.
We are getting a lot of requests for bioassays only as a basis for analytics, which is really for monoclonal antibodies. This is one of my pet peeves: I hate when a regulator says to me, your batch data tells you that this where your specification should be, your specification range, when you have qualified a wider range. That doesn’t make sense to me. We have qualified a wider range. It is within ICH or it is within a set of standards. Tightening it for us doesn’t make it any better. And I can tell you, and many of you have [the same situation], where the number of specification criteria that you have to adhere to for one particular test is huge. In one case, we have 24 separate specification criteria.

We make the product one way and we make it in one place, and have been for a long time. Yet because of arbitrary regulatory needs, we have to adhere to 24 separate specifications. We have to figure out a way to change that. That just is ludicrous. I will leave the other ones here for now.

**Inconsistent Implementation**

There is some inconsistent implementation. It is not just the regulations or the guidances in some countries, but it is actually in the inconsistent application. During the QbD initiative, what industry found was that we would go forward with a quality-by-design approach, where we had good process understanding and product knowledge, and we found that different regions around the world would have different views on how those regulations or those guidances should be applied. And we ended up with some significant concerns.

In fact, the agreements in principle did not reflect the practice. So we have agreements in principle, but when the assessors took a look at it, they decided something different. Part of the reason for that is that a lot of our assessors and inspectors are trying to look for problems, not necessarily look at the big picture.

So there is this disconnect in my view between, I would say, where the higher end of our regulatory bodies are and the folks doing the inspections and assessments. And that can be fixed. That is an educational opportunity for us that we probably need to do better.

I have some inconsistent regulatory expectations listed here as well. One of them is the inspectional review criteria. We are seeing an awful lot of scope creep. Inspection information traditionally and conventionally is migrating to review. And that is trouble, because it is a double indemnity. You could get hit twice for the same thing, and that does not seem to make a whole lot of sense.
Magnitude of the Challenge

Magnitude of the challenge: I have two examples. One is an analytical example. The company wants to take 22 mobile phases, nine columns, and the average run time is 45 minutes for their methods – and basically reduce that to two mobile phases, one column, with an average run time of 3 minutes. There should be a huge savings in doing that. That is for a number of APIs – same methodology.

These products are sold in 174 countries. Implementing that change requires 6,364 national license changes. This is part of the concern that we have.

Magnitude of the Challenge: An Analytical Example

Consolidation of testing methods for a wide range of different products among 20 different APIs to optimize operations using a single “always on” method

- These products are sold in 174 countries
- Implementation requires changing 6364 National Licenses!

Lets do another example – a stability example: In my opinion, stability is confirmatory. You are confirming that your product is stable through its life expectancy, through its expiry. In many cases, when we file post-approval changes around the world, we are being asked to adhere to stability requirements that have no value at all.

So in this particular case, number 1, this is the cost of stability commitments. I just took 29 examples, with a cost ranging from $1.0 to $4.5 million to run the stability studies. And the total cost was $81.2 million. Those gave us no better assurance of quality than if we had not run them. It was a box checking exercise.

Same thing for this table on the cost of stability studies for post-approval changes. I looked at 68 post-approval changes, which affected 2,791 submissions. The changes requiring extraneous stability – I called it extraneous because I didn’t think it was necessary, because I didn’t think it would add any value – were 47 of those 68, which affected about 1,924 submissions.

Total cost of stability per change was between $.25 million and $1.5 million, and the total cost $38.7 million. So the high cost of medicines – part of it is here. It is not necessary. We have science to justify that we do not need it. And by the way, we own stability in our industry. We own it. If we find a stability failure, we have an obligation to notify everybody. It is a problem for us as much as it is for anybody else….
Reflection of Divergence

[Reviewer] queries are not necessarily a great measure of whether or not you have divergence. For the sake of argument, I went back and looked at some of these examples. These are the differences we see for some products.

I just want you to look at this one. This one really caught me. This is a small molecule: 19 from the rapporteur, 122 from the co-rapporteur. What are they thinking? I don’t get it. You can see that the numbers vary. I think that I went and looked at the actual numbers. I believe that less than 20% of the queries that I identified from each of these were the same….

This takes a lot of time. I think we can do better. We can collaborate more. We can engage more. We can do more joint meetings and hopefully eliminate some of this.

By the way, I am not blaming the regulators. I am blaming us as much as the regulators. It is part and parcel of how we present the information, as much as it is how they receive it, and understanding what they are receiving.

The New Quality Paradigm

So to close, the new quality paradigm is about transformative innovation, transparency and collaboration. ISPE can play a huge role in this. I think it has already, and I think it should continue to do that – particularly when it comes down to certain regulatory expectations or mechanistic understanding of our processes and improving our justification for clinically relevant specification criteria.

And finally, especially when we have acceleration and partnerships, we absolutely have to work more closely on harmonizing some of the criteria we are working with.