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Session 4: Facilitating Generic Drug Approvals by Improving Development and Regulatory Predictability

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Co-Moderators:

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Markham Luke, MD, PhD: (Talking off podium)

So, everyone, back to your seats and we are going to start. I just got notification from Shivangi to go start, so we are going to start. We can continue the dialogue that we have and it's great that there is networking at noon when we break for lunch and it is encouraged especially for in person attendees. I guess it's hard to network if you are not in person although they can chat with each other. Ok.

Welcome. This is our session 4, facilitating generic drug approvals by improving development and regulatory predictability. I'm one of the co-moderators, Markham Luke, I'm the director for the Division of Therapeutic Performance One in the Office of Research and Standards in the Office of Generic Drugs. My colleague, Billy Smith, is a research scientist from DPQR V, OPQR in the Office of Pharmaceutical Quality Research in Office of Pharmaceutical Quality and CDER and FDA. You'll notice the heavy presence of our quality colleagues because of the topic that we're going to discuss.

This is a really cool topic. This session will focus on identifying scientific and technical challenges that contribute to multi-cycle reviews. And the emphasis is on multi. And we're trying to reduce the multi to make multi as small as possible for certain complex generic drug products with particular attention to dosage forms, and analytical domains where multiple review cycles may occur. Discussions will center in identifying targeted research, enhanced quality management systems, methodological standardization, or new validation approaches that could reduce uncertainties related to product characterization or regulatory assessment. Panelists will also consider enhancements to current tools or

approaches to address these challenges and what additional scientific research should be prioritized. And emphasis is on additional research. So as all of these sessions that we have at this workshop. And so as folks listen to each other, think about, "Hey, that point you made was great, but how do we change that into an actionable research item?" So these are key things for consideration for our panel.

So I'm going to introduce the speakers, the panel participants, and we'll start with the industry folks, and then we're going to have folks, again, I'm going to go back around, and then industry folks are going to give five-minute introductions of themselves, and then some of our FDA panelists will also have some talks prepared, highlighting some of the expertise that FDA has channeled into this, including some of the management initiatives, etc.

So we'll start with Dr. Clare Butler. Clare is sitting to my left over here. She holds a bachelor's and PhD in pharmacology from University College in Dublin and works as a principal scientist within Teva's global inhalation team. She has extensive experience in analytical method development and validation with strong focus and realistic and clinically relevant approaches to in vitro in vivo correlation. She's expert at in vivo clinical preclinical models and mechanistic modelling supporting the development of inhaled or OINDP products for pharmaceutical products.

And then online we have Praveen Chappa. Praveen serves as Group Head for Material Science and Special Analytics at Sandoz. And he's based in in Hyderabad in India. His focus is on oral solid dosage form development programs, and his expertise are deformulation, preformulation, and seamless characterization. He's had prior roles in a variety of pharmaceutical companies, including Mylan, Fresenius Kabi, Dr. Reddy's, and Novugen.

We also have from industry Dr. Andrew Cooper, who was introduced in the last panel. I'm just going to briefly say that he is from Viatris, and that I got the pronunciation correct, based in Sandwich, UK. That’s where our bread comes from. And then he holds a PhD in pharmaceutical analysis from University of Bath.

And then we have Dr. Niraj Mehta. He's Senior Vice President of Quality Compliance and Sustainability at Lupin Pharmaceuticals. He is the Global Quality Compliance Organization lead. And in that role, he oversees auditing investigations, GMP training, permanent inspection readiness, regulatory intelligence, and governance of quality council activities and metrics. Dr. Mehta has been previously at Merck, where he was responsible for external policy management. And he's also spent over a decade at FDA in roles, various

roles within the CDER and Office of Commissioner. Welcome to our scientists and folks from industry.

From FDA, I'm going to introduce each of you as well. First, we have Dr. William Smith, or better known as Billy. He is a research scientist in the Division of Product Quality Research, and he works on complex drug formulations from topical injectables and polymer devices. And he manages the micrometrics particle size lab. And I think more recently, you've been working on manufacturing facility assessments. He has his BS from Evergreen State College, and he has a PhD from the Colorado School of Mines.

We have Dr. Brock Roughton. He is the acting director for the Division of Pharmaceutical Quality IX, Office of Pharmaceutical Assessment II, in Office of pharmaceutical quality. He is focused on initial IND submission reviews, post-approval changes for ANDAs, and he's been at FDA since 2014.

We have Dr. Eric Twum. Eric is a regulatory specialist in the OPQ, and his focus is on the evaluation of pharmaceutical quality systems. And most recently you'll hear from him, he is very much focused on quality management maturity, or QMM programs, and holds a PhD in computational biology from George Mason in Virginia, here, for those that know George Mason.

Then we have Dr. Cameron Smith. Cameron is a supervisory pharmaceutical scientist in the Division of Product Quality Assessment IV in the Office of Product Quality Assessment I in Office of Pharmaceutical Quality, and he started his FDA career also in 2014 as a drug product reviewer, and he has a PhD from the University of Cambridge in Cambridge, UK. And he also has done post-doctoral work in the University of Utah in Salt Lake City.

And then we have, after Cameron, we have Dr. Bob Berendt. Bob is a supervisor of pharmaceutical scientists in the Office of Pharmaceutical Quality I within the Office of Pharmaceutical Quality. Dr. Berendt and I have worked together for many years and his main focus is on ANDA submissions and review a variety of DMFs. And he's also been heavily invested in the pre-ANDA process with us in the Office of Generic Drugs.

And then representing OGD from the Office of Bioequivalence is Dr. Utpal Munshi, he's the Division Director for Division of Bioequivalence I in the Office of Bioequivalence, Office of Generic Drugs. Utpal's been in DBI since 2007, and he leads his scientists in the regulatory review and assessment of bioequivalence in ANDAs. His PhD was received from University of Michigan, and he has also worked in NCI prior to joining the division of Bioequivalence I.

With that, I'm going to start with some brief talks from the folks…progress to the next slide. Or do I advance? Here we go. We were actually going to have Clare give her talk, followed by.. I guess we have these slided queued up in a different order. We can adapt to this. Can

we go back? So, we'll have Brock give his talk then, and then so we have two FDA talks followed by introductions from the various industry speakers. Go ahead, Brock.

Brock Roughton, PhD: Thank you, Markham. Good morning, everyone. Good to be with you. Yeah, my name is Brock. And I just wanted to take a few minutes at the start to kind of look at things from Office of Pharmaceutical Quality's perspective when we're looking at, you know, complex generic products and some specific issues that, as Markham alluded to, may lead to multiple review cycles. So looking at things like non-compendial methods, that comparison to the test and reference, which came up in the last session as well, and setting acceptance criteria.

So, I believe that we have the same goal from both the applicant's perspective and a reviewer's perspective, which is that we want to assure the availability of quality, complex, generic drug products. So how do we get there in an ideal kind of roadmap? So FDA has put a lot of work and continues to put work into coming up with product specific guidance or PSG for these types of products. And so, you know, this is an iterative development and it's an opportunity for us to identify at an early stage, you know, what are the gaps in our understanding and where could we have research here to help us when we get our first applications coming through the door.

Once these are published, then, you know, the applicant is looking at them, interpreting, and trying to implement them in their development program, which can guide their identification of the quality target product profile, you know, their product development strategy that ultimately ends up in the PDR in the submission and, you know, putting together their control strategy for the product. And then, you know, as this is going on, there's the opportunity through the pre-ANDA program for meetings and correspondence with FDA, including, you know, if there's specific questions for OPQ, and this also gives us the opportunity, if there are some still areas that are unclear on our side, we can start thinking about, you know, what are the knowledge gaps still there so that we're ready when the review comes that we can make the best review decisions.

And so then, you know, once the application comes in, once the review is written, do we reach the same conclusion? Right? Ideally, we would both be on the same page that, yes, this characterization here has supported the demonstration of bioequivalence and pharmaceutical equivalence, and that we have adequate assurance of the drug product quality throughout the life cycle of the drug product.

So that's kind of the roadmap. So I'll kind of pose some questions maybe from applicant's perspective and then from FDA's perspective to help us get there. So again, we have the PSG. We want to have a first cycle approval of a quality drug product. So let's say you look at that PSG and there's an attribute listed there for characterization. And so, as an

applicant, I'd be asking, what is the method that I think would be the best to characterize this product? Then what is the validation approach that I'm going to take for this method to demonstrate that it's suitable for its intended use? And then once I get that data, you know, from characterizing the reference product and my own product, the test product, how am I going to compare these results to show that this method.. characterization approach is actually demonstrating what we expect, the BE and PE?

And then, thinking down the line, for this attribute that we've characterized, is this something that we would need routine quality control for? And, maybe this method that we're using for characterization is not really suitable for a QC test. So could a surrogate test be used instead? And then when I go to set the acceptance criteria, how do I do that? Is there some way, you know, have I, for my development program, have I identified if there's any clinical relevance that can kind of help set this acceptance criteria.

And then, so maybe if there's any uncertainty on those questions, there's different approaches right from the pre-ANDA program, a PDEV meeting to help make sure that the strategy that's going to be taken to demonstrate BE and PE and the strategy for assuring quality are in line with what the FDA is expecting. If you're ready to submit, maybe having a pre-submission meeting to make sure that the package that we're putting together, the data that we've gathered, that that would meet regulatory expectations. And if there's, you know, one specific question that we can target, controlled correspondence offers maybe an efficient route to get that answer and keep things moving.

And then through product development, we've seen kind of what the end product is. Do we have from the beginning that quality target product profile well defined with our CQAs identified? And then at the end of the day, when we put it all together, can we justify how the development studies were selected, how those methods were developed, and how the acceptance criteria were set? And can we put this together in a comprehensive way into the product development reports or looking forward to M4Q(R2), the development summary and justification section?

But there's things we should ask on the FDA side too, so I won't let us get away with not asking questions. So again, if we want to get from the PSG to that first cycle approval, we see that attribute listed in the PSG. Do we have clearly defined expectations for how that method should be validated? And if not, can we identify what sort of research would help us to do that? At the end of the day, can we publish methods or a framework for validation?

And then, looking at this attribute, do we have a clearly defined expectation for whether this is something that we need routine quality control, or is this just needed for that one-time development study? And if we need it for routine quality control, how are we going to judge

whether the acceptance criteria is appropriate or not? Again, there may be opportunities for research here for the clinical relevance of those quality attributes and how big of a range in those attributes we can have without getting into a difference in quality.

And then when industry does come and want to have a PDEV meeting, have we already proactively identified where we need research in the PSG development? And do we have those results that can inform meaningful discussion so that we provide the most meaningful input that we can? And similarly, on the pre-sub side, do we know what we want to see in the application, and can we clearly communicate that?

And then, yeah, we did get into this a little bit in the last session. This is a question that can come up when we're looking at the test compared to the reference and saying, are they the same or are they similar? So like a hypothetical attribute we're looking at that we've characterized and we have several batches of the test versus several batches of the reference, and we're looking at that in our review and we're saying, are they the same? So, maybe example A is pretty straightforward; we could say yes, but then what if the distribution is wider for the test versus the reference skewed in a different way compared to the reference, or, as was brought up, we don't have enough availability of the reference to really see that variability in the reference to compare against the variability in the test. So, how can we move forward from here? And, I'd like us to maybe think about, discuss, what, how can research help here? You know, do we need to just look at this one attribute in a silo or can we look at like a totality of evidence approach? So if we do get into like example B, C, or D, we're not kind of stuck there. So with that, thank you for your attention and looking forward to discussing more.

Markham Luke, MD, PhD: Thank you, Brock. Next, we have Eric Twum. Eric.

Eric Twum, PhD: All right. Thank you, Markham, for the opportunity to be here this morning. Good morning, everyone. My name is Eric Twum. I'm a regulatory specialist in the FDA Office of Quality Surveillance, under the Office of Pharmaceutical Quality. And it's an honor to stand before you this morning to speak on quality management maturity, or QMM.

Over the next few minutes, I'll be sharing how establishments with mature quality management practices can be better positioned to systematically reduce errors, minimize waste, and sustain long-term performance. Ultimately, it is my hope that this presentation will further deepen our understanding of QMM as not only a framework for driving business excellence, but as one which establishments could embrace as they look to avoid some of the facility-related quality and manufacturing challenges that we've seen impact review cycles.

So, to kick things off here, I'd like to share a few quick facts about QMM. First, QMM is a framework which measures behaviors and practices that sustain an establishment's quality culture, promote supply chain reliability, and also enhance the operation of the quality system. It examines an approach to quality management that goes beyond meeting the regulatory expectations, one that strives for excellence. However, QMM is not a substitute for regulatory compliance. It does not replace CGMP inspections or replace quality testing. It is actually a mindset that translates into an establishment's quality behaviors and practices, which we assess across five key practice areas, which include management commitment to quality, business continuity, advanced pharmaceutical quality systems, technical excellence, and employee engagement and empowerment.

So, again, just to get a high overview or like a big picture view of QMM. High maturity is reached when an establishment successfully integrates business and manufacturing operations with quality management practices and technological advancement, all of them working together to optimize product quality, enhance supply chain reliability and drive continual improvement. So the big connecting piece here is really integration. Higher maturity happens when these elements stop functioning as separate silos and they start reinforcing each other.

So, over the next couple of slides, I'm going to be sharing some of the data that we've had based on the previous QMM assessment that we've performed. So based on the lesson that we learned on previous assessment cohorts, basically I'm going to be walking through the next couple of slides, sharing two specific areas in which QMM could be at play. In essence, what I'm saying is that areas which can highlight QMM as an opportunity for firms to really achieve positive business outcomes. However, before I proceed, I think I'll throw in a quick word of caution here. The practices that I'm going to share in the next couple of slides were not unique to one firm. They were scattered across a number of firms. And also the goal here is not really to be prescriptive here, but it's really sort of to hold up a mirror to you, sort of, so that you can kind of look at where you are and then maybe think about where you want to go.

So, let's talk about operational reliability. Operational reliability is the ability of a firm to consistently maintain operations with minimal disruption and includes the ability to manage resources efficiently, maintain productivity, and deliver quality products or services. And preventive maintenance is a key operation for ensuring operational reliability. So I have on this slide here our cool cartoon character here that I made up to sum up two fundamental ways that establishments approach preventive maintenance or PMs based on what we've seen in previous QMM cohorts.

In the higher maturity setting, as you can see on the left, preventive maintenance is fundamentally proactive and dynamic. Basically, the establishment has moved beyond the vendor's manual. They are using their own dynamic data to build an intelligent risk-based maintenance system. In the lower maturity firms, as you can see on the right here, an approach to PM is quite opposite and unfortunately too familiar to some of us. That is, you have a PM program that is basically reactive in nature and does not really seek to prevent issues. In essence, adopting a generic one-size-fits-all approach or schedule, that doesn't account for your specific operating conditions and also production tempo is lower maturity.

So in high maturity firms, the approach that I mentioned, that is the proactive approach to PMs, is likely to optimize preventive maintenance, maximize equipment reliability, and also ensure that production flow is smooth. For example, one practice that we've seen high maturity firms actually implement is that they integrate metrics like mean time to failure or MTTF and mean time between failures or MTBF into their production scheduling based on their own historical data. MTTF is actually a metric that measures the average lifespan of a non-reparable asset from the moment it is put into service until it completely fails, while MTBF measures the average time it lies between the inheritable failures of an irreparable system during normal operating hours. Typically, high maturity firms look at MTBF and then they begin to ask questions around maybe why are we failing, why are we having equipment breakdowns every 600 hours instead of 800 hours? Then they look at MTTF to tactically replace those parts that may be prone to failure on the schedule before they experience a batch failure on equipment breakdown. We've also seen that in high maturity firms, they incorporate risk-based inspections as well into their PM plans so that maintenance decisions are grounded in actual equipment risk instead of generic guidance. On the contrary, as you can see here, in the lower maturity firms or with the lower maturity approach, it can easily lead to frequent equipment breakdowns, production disruptions, which could manifest as part of the larger pattern of facility-related quality issues that we sometimes see in Complete Response Letters.

Now, let's talk about continual improvement, which is simply the idea of doing something better than you did that, you did it yesterday, and then doing that repeatedly. As we may all agree, continual improvement is embedded in what we do as an industry. Again, our cartoon friends here help illustrate the distinct ways lower and higher maturity firms approach continual improvement. Establishments with higher maturity have a strategic, structured approach to continuing improvement. One where the establishment is deliberately and also systematically working towards defined goals. They treat continual improvement as a journey, and they have a clear destination. The journey is guided by, and also supported by, data, which includes both internal and external data. More so, it is

driven by a strong leadership that sets clear risk-based priorities and empowers the teams to implement the improvements.

In lower maturity firms, on the other hand, we see an approach that we kind of sort of liken to a whack-a-mole approach. I don't know whether you've been to an arcade game before, but yeah, it's a fun game to play. But, you know, that is not a good strategy to apply to continual improvement. I can bet you on that. One issue comes up, maybe an audit finding, an SOP deviation, and maybe a training gap, and then you know the firm sort of struggles to kind of knock it down. Maybe the goal is maybe to simply close a CAPA and then forget about it. But we've seen that every time that the firm does this, a new deviation comes up of the same nature that the firm will have to knock down again. So that's how firms with a lower maturity approach continual improvement. They see it as more like short-term wins, something to be gained and something to be benefited from in the immediate term, rather than having a big picture look on it.

So again, let's put this in terms of business outcomes. On the higher maturity side, the strategic approach to continuing improvement is likely to result in sustainable gains and generate long-term value. Again, here's an example of practices used by higher maturity firms to get to this point. They use a rich combination of data, employee feedback, crucial external data, including the voice of the customer, and maybe competitor analysis, customer complaints, and all that. And they use that sort of to drive that process. And then most importantly, they have a dedicated leadership that sets clear priorities and establishes goals that are directly tied to the quality and business objectives. Lower maturity, again, I won't spend my time here, but I think it's pretty much intuitive what it could result in or the potential, very little potential for long-term value, right? And there are examples of practices that we've seen in firms. We've seen a firm where continual improvement is really driven by compliance needs only. There's no dedicated leadership, and there's no way of really prioritizing what to work on. They basically fix the problem in front of them, and then they just move on.

So as I conclude this talk, I think we can take away a few things with us. First, quality is really a tale of two cultures. Really, it is. On one side, you have establishments that treat quality as a regulatory checkbox, something maybe to satisfy an inspector, maybe pass an audit or maybe clear a pre-approval inspection. And then on the other side, you have those establishments that have really embedded quality as a strategic driver for operational excellence. One that can be really leveraged to gain a competitive advantage, including benefiting from regulatory flexibility and the ICH Q12, which my colleague from OQS, Torrey Ward, spoke on yesterday.

The difference between these two cultures can really be evident in how equipment is maintained, how continual improvement is structured, and also ultimately in business outcomes. And these are tangible outcomes. Higher maturity in operational reliability, continued improvement, and many other things can help contribute to more first cycle approvals, less waste from failed batches, and more consistent supply to patients. And these outcomes do not only matter to the generic business, where there can be razor-thin margins. These outcomes matter to the public health mission we all share, so I'll leave you with these two questions. Where does your establishment stand, and where do you want to be? Thank you.

Markham Luke, MD, PhD: Thank you, Eric. So our next, this brings us to our industry participants, and they're going to do quick introductions for each. Clare, I think we have you up first.

Clare Butler, PhD: Good morning, everyone. My name is Clare Butler. As Markham mentioned, I work with Teva Pharmaceuticals within the Global Respiratory R&D team. I'm here from Ireland, where the weather is certainly not as nice as it is here, so I'm delighted to be here for the weather, not just the conference, if I'm honest. But yeah, so Markham alluded to my background. So by way of training, I'm a pharmacologist, but I've worked for the last 10 years or so on the development and validation of analytical methods, tech transfer. More recently, my focus has been on establishing IVIVC for respiratory products and the development of more physiologically relevant analytical methods such as realistic APSD and dissolution.

So my goal here today is not just to highlight or establish the challenges that we have encountered, which have led historically to CRLs and multiple review cycles, but also to establish what we perceive are going to be challenges in the future, with the application of new sciences and the evolutions of PSGs that we've seen over the last number of years.

So one particular challenge that we have encountered before are issues where we receive deficiencies following tentative approval. And so you say, give me an example. So these aren't just necessarily label changes. These also pertain to things like application of the brand product to a new patient cohort, such as a pediatric population, which does create quite a challenge for us as a generic group and having to then do more clinical studies. Something else that we have encountered are the changes or upgrades from minor DRLs to major DRLs after having submitted requested leachable data for which we've established that there are no toxicity or safety concerns. With the TA letters, these are specifically difficult to manage, especially when there's a large time gap between tentative approval and full approval. So there are certainly challenges that we have experienced. So in terms of then, what could be done to focus on research around these challenges, are there ways

that we can better as a sponsor work with FDA to predict these situations, so that we can then assign resources more proficiently to deal with these if they come up. Another potential suggestion would be where we have DRLs and DRL clarification meetings. Are there ways in which these clarification meetings could be changed in terms of the scope of just merely understanding the comprehension of the wording in these DRLs to more scientific and technically focused conversations to potentially prevent a CRL happening.

Another challenge that we've definitely encountered before in the past is where we have post-approval RLD divergences. So specifically when the brand RLD has a user set change, this can be particularly challenging for us in terms of having to then potentially look at redesign of a product, a whole new post-approval submission, looking at human factor studies, etc. And more of a challenge when we know that the bioequivalence of the product in terms of formulation isn't affected, the clinical efficacy is not affected. So there are the regulatory challenges, but patient centricity is at the focus of everything that we do at Teva, and it's particularly close to my heart. And in instances where there may be only one generic available to a patient population suffering from a specific disease, instances where there are RLD divergences could potentially remove the access to this generic product while we actually focus on the challenge and how we overcome it based on the risk at hand. So again, research focuses that we could look at for this, and they're just suggestions, are there quality management systems where we could standardize communications around these changes and look at how we deal with them between sponsor and FDA based on risk, especially where BE, like I said, is not affected. Are there other approaches we can apply to mitigate these risks, other than having to go back and change the device, redesign and do new studies, et cetera? It also poses the question, where you have an RLD there available to the public, should the changes or RLD divergences be viewed slightly differently when these RLDs serve as reference products for multiple generics that are already on the market? And how established does a generic product need to be before we then ask the chicken and egg question of analytical life cycle management for the generic product. And I suppose this is particularly pertinent with respect to new green propellants.

With respect to IVBE and Q3 methodology that we have, the Q3 methodology that we've seen implemented in new PSGs over the last number of years where there are CE waiver approaches to establishing bioequivalence. So I think with Q3, the PSGs are extremely clear in terms of what descriptors we need to compare. I think where the question is and where there's room to improve here or room to align more clearly, is what constitutes similar versus very different when we're actually comparing the data sets that are generated from this Q3 analysis? Again, you'll ask, well, give me a specific example. So, when you have something like a solution-based PMDI, where the ask is to compare

something based on image. It's, what is the expectation, not only just in terms of method, but what type of analysis is expected? Is it literally a comparison from A to B? And what do these Q3 methods serve as in terms of mitigating risk when we have other methods such as realistic APSD, which are far more discriminatory for solution-based PMDIs? And when we have to do a PK anyway, it would be just the question, what is the expectation from Q3 dataset comparison perspective?

I think with the dissolution methods that have been introduced into the PSGs for OINDP products in lieu of clinical endpoint studies, not having a universally accepted method isn't really the challenge. I think it's establishing or clarifying within the PSGs, how bio-relevant is bio-relevant enough. So I think where we can recapitulate the in vivo scenario as best as we possibly can, how far do we need to go before the methodology is accepted? And I think some clarity around that would be really, really useful for industry.

And the last one really I just wanted to touch on is, where we see the evolution of PSGs to remove clinical endpoint studies, where then is the expectation on drug product characterization studies such as patient use studies? So where we would have generally done clinical endpoint studies, obtained retains from those studies to do patient characterization studies, where did those characterization studies lie in the totality of evidence in terms of establishing BE? And perhaps there is a way we could further align there in developing a more explicit risk-based framework to guide sponsors as to which one of these DPCs are necessary versus not in the absence of a clinical endpoint study. So, that's it for me. Thank you very much.

Markham Luke, MD, PhD: Thank you, Clare. We're next going online. We have Praveen Chappa from Hyderabad. Go ahead, Praveen.

MrPraveen Chappa: Alright, good morning everyone. Hope you're hearing me and then able to see my screen. Hello?

Markham Luke, MD, PhD: Yeah, go ahead.

Praveen Chappa, PhD: OK, alright, great. Good morning, everyone. I'm Praveen from Sandoz Development Centre. I serve as a group head here and looking after oral solid form doses development. And I'm passionate about how we improve, how we can improve the quality of the dossier that we submit and targeting to have a first cycle approval. And today I would like to share some practical insights from across any review cycles that we have seen across the products that we received from FDA. Before I go further, a quick disclaimer, and these perspectives reflect my own reviews and views and experiences intended to discuss in this forum.

With that, let me start a quick what we offer deficiencies landscape that we could see across the projects and then the discipline. So the predominantly what we see in quality and then the bioequivalence and then labeling. In the quality discipline, the questions are quite heavy. And looking at a breakdown of the quality discipline, the major questions are from the drug product, manufacturing and drug substance. Recently, we could see a lot of deficiencies around biopharmaceutics, and these are related to setting the specifications, discriminative ability of dissolution methods, topics on nitrosamines and E&L topics, and the topics on manufacturing processes that we could see predominantly across the quality discipline.

And I would like to highlight key challenges and opportunities which directly contribute to a repeated review cycle along with the potential opportunities. And before this session, we talked about the challenges on complex analytics and related opportunities in terms of sameness characterization, maybe in vitro metrologies or BE studies, as well as in yesterday we talked about the complex impurities about nitrosamines. Apart from these two areas, we could see a lot of questions around dissolutions, particularly the discriminative ability and linking to clinical performance. This is quite a reoccurring deficiency which we could look at as one of the potential that we could see across the products. And other part we could see on the tightening of the specifications, particularly the critical quality attributes. It could be a water content or of course the dissolution limits, essay or polymorphic form specifications, right? And the other part that we traditionally cover is manufacturing part, which is something related to how we connect to critical attributes like process, material, to CQAs and then relationship and quantitatively. All these, when we look at deeply, these are not like an isolated deficiencies. And when we look at all this data, then we understood, looks there is some systematic a gap or alignment to understanding between applicant and then the the PA which which possibly kind of a discussion which we can able to continue as as we move on in the session.

When you look at, in summary, across these deficiencies, there are a lot of gaps and understanding around PSGs and then the specifications and then lack of standardized, bio-predictive dissolutions, which potentially may make a gap in understanding or in terms of guidance. For suppose to take it to bio-relevant dissolutions. The expectation is around 80% release, but still we should have a discrimination ability, which somewhere this understanding is misaligning between reviewers and then applicants, where we may need to strengthen and and bring a framework around on the expectations very clearly. And and we discussed a lot around topics on complex generics. And when it comes to specifications, which somewhere we need, and we see a repeated deficiencies around tightening of the specification limits, maybe in case we have an alignment on certain expectations, bringing some statistical approaches, which really brings a lot of clarity to the

applicants. So with this, we would be able to really enhance and then align with our dossiers quality in line with the expectations and that eventually help us to reduce the review cycles and then help our applicants to bring the generic products to the market. With that, I'm just getting it going. I'll be there. Yeah, thank you.

Markham Luke, MD, PhD: Thank you, Praveen. And your assessment of around 80% quality related CRL issues aligns with FDA's as well, our assessment. So next up we have Andy Cooper. Andy, you want to give your 5 minutes? Appreciate it. Thank you.

Andrew Cooper, PhD: Yeah. Okay, I think you'll find that my intro slides are more of a prompt to me than they are for you to see, but we'll see. Yeah, so I'll try to keep them very brief, actually. So I think you've already had me introduced twice. And I guess why am I in this session? Well, it's probably more to do with my background than my current role, actually. Because my background is in pharmaceutical analysis, I've been focused on complex products throughout my career. And before my current role, I was the head of analytical materials science for respiratory products in Viatris. And I kind of lived through some of our key respiratory product ANDA submissions. So I'm drawing a little bit on some of that experience. So I've just got a couple of kind of bullet points, a couple of things we've kind of pulled out of that experience, which certainly have the potential to cause extra review cycles.

And extractables and leachables actually came top of our list. And by way of apologizing for my imposter syndrome, I have to point out that our technical lead in this area, Lance Molnar, is, I think, probably still in the room. So he might come to the floor mic if I say something that he doesn't agree with. But we do find that extractables and leachables is a recurring source of review issues, including complete response issues in complex product submissions. And, to be honest, from an industry perspective, the agency comments that we get sometimes appear quite unpredictable and inconsistent, and I think that there's possibly a root cause for that, which is that we've got multiple current sources of guidance, multiple USP chapters, and historical PQRI output, and those are not particularly well aligned. But there is, I think, a good opportunity here. There's the ICH Q3E guidance, which has now been worked through into final state, and that's being implemented in 2027. So that provides, I think, an opportunity for industry and the agency to really get together and improve our alignment of expectations around the interpretation of that. I know from the kind of industry side, the E&L Safety Information (ELSI) consortium, I think, is planning to arrange some workshops with the intention of attracting regulatory interest into those conversations. There might be a role for CRCG in this as well. And so hopefully this is something where we can move forward together, because I think historically it's been a very, very difficult area.

And then the second area, a bit more from my own experiences, is around conduct of in vitro BE studies. Now, I can't honestly say that I know that this has caused a CRL, but what I do know is this has come up in inspections at test labs and so therefore has the potential to to find its way into CRLs. And we understand that the agency expects that ICH M10 guidance on bioanalytical methods is considered applicable to in vitro BE studies. And that guidance, I mean, it's fairly recent guidance, but it largely reflects, I think, pretty longstanding practices in bioanalysis and reflects some of the challenges of analyzing low levels of drugs in biological matrices. And of course, a lot of what we're discussing at this workshop is the significant shift in PSGs towards the use of in vitro BE studies as an alternative to in vivo studies. And I think that there probably is an opportunity to look now at ICH M10 and to look at providing more tailored guidance for the conduct of in vitro studies, because they're quite different to an in vivo PK study in terms of what you're analyzing and how you're interpreting the data. And what we hear from what we know from the labs that run these studies is that applying some of those historical bioanalysis practices actually kind of hinder the operation of those studies. And so I think there is an opportunity to maybe reflect on this, maybe even some perhaps paper-based research that just kind of looks at what are the risks around these kind of in vitro methods across the range that are now being used and what is the best way to actually conduct those in terms of the study controls and the way you calibrate those studies. So again, I think this is maybe something that we can look to move forward on. OK, that's I think all I had.

Markham Luke, MD, PhD: Thank you, Andy. Next, we have Doctor Niraj Mehta, Dr. Metha, Niraj from Lupin.

Niraj Mehta, PhD: Thanks, everyone. Good morning again. Niraj Mehta, Lupin. I lead the Global Quality Compliance Group within Lupin, and I've been in that position for a little over a year, but I wanted to thank the agency, Billy, Markham, and the organizers for having me this morning. So it's great to be back at the FDA. Before I start, the typical disclaimer of these views are my own and don't necessarily represent those of Lupin.

Next slide? Got it.

So, I started thinking about this and I was going to do this kind of list of CRL deficiency categories. And then late last night, I decided to go a completely separate way and decided to connect these deficiencies to quality management maturity. So we're going to talk a little bit about what are some of the driving forces within what we see here and some of what Eric touched upon. And without seeing Eric's slides at all and putting together my little script here, it's really interesting of the connectivity that you'll see in the themes, which you should see when you think about something like an initiative like quality management maturity.

So really the way I look at CRLs in this space is kind of, they're more like lagging indicators for QMM, right? So a CRL is not necessarily a failure to meet a GMP requirement, but it's really a failure to establish those robust, proactive, and sustainable quality systems that we're all trying to get to, right? So the theme of what high quality management maturity are, anticipating risks, managing variability, continuous improvement. I think Eric used the term dynamic data, dynamic data-driven decision making, and how that really connects then to reduction of CRL. So I'll go through some of these categories now.

For facility inspections, right, so one of the most critical drivers for CRLs is ineffective quality systems, especially when you look at how organizations may manage investigations, CAPAs. And at a basic level, when you're talking about compliance, you're saying, yes, we address deviations, right? But a mature system really looks into identifying trends early, driving root cause analysis, and implementing CAPAs that really are focused on preventing reoccurrence, right? So simply correcting issues doesn't solve the systemic problems that lead to repeat findings, really. So when you look at things like lab controls and training deficiencies, we can kind of connect those kind of broader to what we talk about culture and governance, right? So mature organizations make decisions that really are focused by data and risk-based thinking and continuous improvement that's embedded into our operations. CRLs really kind of represent execution gaps when you think about them in the context of facility inspections, right? But they're really a lack of proactive quality oversight and accountability in this space.

When we move over to product quality, right, we're moving from the sites into the product quality space here. We are thinking about two specific themes: variability and control strategy, right? So, mature quality management maturity really proactive variability, proactive management of that variability by connecting things like material attributes, process parameters, and even product performance. So, what you're looking at is how do you use the knowledge to proactively manage that variability, right? The second area, when you look at things like raw material and specifications, those less mature systems really rely on kind of poorly justified specifications. Mature systems are really going to look at, again, looking at the science and risk-based approaches, continually refining their specifications, right, based on what that process knowledge actually is. And kind of again, looking at things like supplier oversight and integrating them into your control strategy, right? So the key concept here is shifting from what you would consider more like static specifications to those that are kind of based on knowledge and experience-based control mechanisms in place.

So one of the new linkages that I'll also kind of think about, or at least what we think about, is looking at kind of QMM as the management of emerging risks, right? Things like we had a

really great session on nitrosamines yesterday, extractables and leachables, and really reflecting on the ability to anticipate risk and adopt those kind of those strategies more proactively is the right terminology here, right?

So then we look at CMC. How does the CMC package really demonstrate maturity and sustain performance throughout the life cycle, right? Significant maturity gap is seen between process validation and life cycle management, right? High QMM is where the validation and process are integrated as a part of the life cycle. And opportunities to optimize performance are kind of proactively identified in this case, right?

And in the interest of time, I'll skip right over to devices, right? So when we look at devices, and I'm not a device expert, but we're looking at kind of maturity that's really focused on design and embedding user-centric data, right? So design validation is beyond just the specs again, right? It's mature systems looking at the reliability under real world use conditions. How is a patient using that product and anticipating what that risk is going to be based off of that use in the long term? And you can kind of think of this as more specifically related to kind of human factor engineering, right? You're really using that to define the design which feeds into change management, ensuring decisions that we're making are data-driven across the entire life cycle.

So kind of in summary, when we look across these systems, we're really not thinking about moving into the quality management maturity space when we're not being reactive and we're building it into system design. So the themes are, reactive versus proactive systems. We're talking about compliance-focused being, you know, going back to Eric's whack-a-mole, which is just looking at one individual compliance issue, moving from a compliance-focused world into a science and risk-based decision world. And then static processes versus continuously improving optimization. So I'm not up here to say that advancing QMM is going to avoid CRLs, but I think if you think about building resilient systems, you're able to kind of deliver those high quality products that we're looking for in this space. So thank you.

Markham Luke, MD, PhD: Thank you. And then just a hand to all of our industry presenters. Thank you both in the room and virtually. So next, Billy Smith. Dr. Smith is going to lead the discussion.

William "Billy" Smith, PhD (Moderator): Hello, check, check, check. Okay, so I want to thank the industry speakers first and foremost for your candor in helping us kind of look at some of the root causes or the things that you kind of are seeing as leading to these kind of multiple cycle and CRLs. So maybe given the context of what you've all just heard, I'm just going to kind of turn it over to perhaps some of our FDA panelists and maybe I'll start at the

end there with Utpal. Do you have anything you want to add as far as, in the context of those kind of top deficiency types, what you see from your side as far as like BE?

Utpal Munshi, PhD: Yeah, sure. No, thank you. So I think, you know, there are several things. I think the types of deficiencies we see that are common depends on the type of product. But in general, whether it's complex or non-complex, I think some fundamental things like not providing raw data for certain studies, not justifying deviations from product specific guidances. That's another thing that we see. Another thing that, you know, I think more related to the discussion today for complex products is, you know, applicants will come in and they'll come in with their proposal in the PDEV stage. And then when we actually get the ANDA in-house, we find that things are changed. And so what we discussed in the PDEV stage is a little bit different. And so then that takes a little bit more time for us to review. So it's not a deficiency per se, but in the spirit of, you know, trying to reduce time to approval, I would say that if at all possible, sort of staying within what was discussed in the PDEV meeting is helpful. And if not, then certainly providing the justification for those deviations would be important as well. Yeah, thank you.

William "Billy" Smith, PhD: Thanks. And now moving maybe towards our QC side, our quality side, I think it does seem like there is kind of this question towards, in PDEV and that kind of stuff, when we're looking at using methodologies for BE, and a lot of times those things are kind of focused in that direction, but then we start translating into, you know, the quality side, where maybe during PDEV you don't have your full analytical method validation package done for a specific CQA or specific specification set. I just wonder, for all of our quality people, and maybe starting with Bob, if you have some kind of input on what we've seen from our industry folks here.

Bob Berendt, PhD: Thanks, Billy. So, you know, my comment isn't specific to the analytical side of things, but I did appreciate that Clare addressed it and some of the other speakers addressed it too, that, you know, we're all here today to talk about accessibility to complex generic products, and certainly that starts with strong development so that the ANDA package itself can be submitted and then approved. But we do want to think about the life cycle overall, and the life cycle of the generic, the life cycle of the RLD, and how all of that affects accessibility for the generic products. Certainly, we've seen issues that come up in the pre-ANDA discussion space that will have long-term effects for the ability for the product to not only be approved as a generic, but to remain on the market, to be able to navigate excipient supply chains, changes to the device, constituent parts. So I think that, again, it's, you know, and some of those post-approval changes also having strong scientific understanding that the agency is working on an industry as well to help publish product-specific guidances. Those product-specific guidances are helpful overall for the

life cycle of the product, post-approval as well. So I just, you know, I welcome continued discussion, not just on the pre-approval side, but the post-approval side.

Cameron Smith, PhD: Hi, I'm Cameron Smith from OPQ as well. So from my perspective, what I see is that, especially for complex products, there's three main areas where we see recurring deficiencies: demonstration of active ingredient sameness, demonstration of the comparative physicochemical properties (these Q3 properties), and also qualification of impurity limits. And we heard a lot of themes around those three areas this morning, especially various types and types of impurities. People mentioned extractable leachables, nitrosamines, they could all fit under that category.

And so what we see, I think, is certainly the knowledge and experience of the applicants can have an effect on the quality of their submission. And so then there's a balance really between how much information we should put out in PSGs in terms of information to help industry submit a better quality application and also a balance between industry asking questions back to the agency via the various communication methods we have. PDEV meetings and controlled correspondence which have been discussed. So our guidance PSGs tend to provide recommendations on attributes that need to be characterized for these types of studies, but we don't tend to provide information on exactly what analytical methods might need to be used. And I think traditionally we've stayed away from doing that because we want to give industry the freedom to be able to come up with their own methods and provide their own justification for those methods. And that allows the advancement of technology to be continually accepted by the agency.

And then from the meetings perspective, I think we certainly over the years seen a lot of good utilization of the PDEV meetings and control correspondence. I would certainly encourage industry folks to continue asking questions by that mechanism. But I would also, in more recent times, we've had some more recent examples of pre-submission meetings where they've been quite useful. So, once you've developed your product, it can be quite useful to come back to the agency with a pre-submission meeting and say… just give a last check to see the structure and format of the information you're planning to submit in your ANDA. We can, although we can't obviously provide any review of that data, we can certainly provide advice on if there's any gaps in the data that's been submitted, for example. So yeah, so I think I'll finish there. Thanks.

Markham Luke, MD, PhD: Cameron, I think that's a great point. The best pre-submission meetings are those that have gone through the rigor of having other pre-development meetings. I think that it's part of a package of meetings with FDA before the ANDA submission. It is helpful to have a pre-submission meeting.

Eric Twum, PhD: So I think our introductory talks have already provided the background and a segue for us to explore deeper in terms of basically looking at the quality management system as a proactive system, as a system that connects all the different pieces and really helps enhance the technical side. I know that a lot of discussions have taken place between yesterday and today about how many things can be done right. But I think generally we are getting a sense of what the quality issues are. A lot of them really stem from a lack of knowledge about a specific process or a specific method or maybe specification. So I think as the discussions progress, it will be interesting to explore further and deeper what are some of the missing challenges that firms have with respect to bringing that quality maturity thinking to applying or enhancing some of the technical aspects of the ANDA process? Thank you.

Markham Luke, MD, PhD: Eric, there may be a research opportunity there, like you can take all the 483s and seeing, okay, well, what was the failure in the QMM that led to that 483 and then accumulate that kind of knowledge? Is that something that OPQ would be interested in pursuing further? So that could be interesting.

Eric Twum, PhD: I think so. And I think we've already seen a snippet of that data. We've seen instances, and that is why my talk focused and highlighted the preventive maintenance, but we've seen instances where CRLs were issued out because equipments were not maintained properly and instances where there's a massive buildup of residue in HEPA filters and the firms say, "Hey, I was following the supplier's manual." So certainly there's a lot of data out there and you know, we are happy to explore the data for that to really drill down to other areas. Thank you.

William "Billy" Smith, PhD: Brock, you got input?

Brock Roughton, PhD: Sure. I mean, I already spoke a lot, but I would just point out one thing that I thought was very informative from hearing from you all, and that was each of you pointed out that extractable/leachables are kind of a pain point. So maybe we could think for that area in particular, what sort of research could help with setting regulatory expectations, making those more clear, making, when you do those studies, that kind of that framework is clearer so we can not have that be such a pain point in the future.

Markham Luke, MD, PhD: Yeah, and it was mentioned we have some things coming down the pike, right? A container closure guidance is on its way out. It's on the list of pending guidances that are finalizing and the ICH Q3E that was mentioned. So I think that that did come out last December, but hopefully it will finalize in 2027. Thanks..

William "Billy" Smith, PhD: Great. So maybe turning a little bit away from this, but keeping the heart of the issue. As far as we've seen these kind of issues from both sides leading to

deficiency. And one of the hearts of at least the next session is going to be specifically on PSG, but in some way, harmonizing the expectations and the communication between the firms and the FDA would be really nice. And I just want to know from the industry's point of view, obviously, as Cameron said, we can't make the PSGs overly descriptive just to leave it open for new analytical techniques, non-compendial stuff. But I just wonder, from a research perspective, how effective is it to go and look at FDA publications? Are there areas where you think things are still lacking as far as the APSD stuff or kind of anywhere in the area as far as what's that next place that you would go to look for additional information outside of the PSG from the agency.

(Audience Member): I just would like to ask a question or a request to the FDA on the previous point. In the complex world, what we also see is we also would like the agency to understand complex products, development of complex products, how the generic drugs really get into it in a very short period of time. You have to develop, you have to submit. And of course we do understand the maintenance and the lifecycle management. This is very, very important. But one of the areas I really want people to look at it, because when we present, we are presenting with a certain amount of knowledge. We don't have ample amount of the knowledge. We learn more about this complex and we produce more and more. That's been happening. Like when we make the batches and present data, the data probably looks good, but there could be some variables post-approval that we do not anticipate early in advance of our development program. So I think one of the things I really would like the agency to look at is yes, as is a pre-development meetings, we come up with a certain knowledge. Our knowledge now increases as we go into more. So there should be further communication, even post CRLs. There could be further communication post-approval. What are the challenges we are facing as we're learning more and more? Should be considered. That's all my request.

William "Billy" Smith, PhD: Thank you very much, and for the record can we get your name and affiliation?

(Audience Member): (low audio)

William "Billy" Smith, PhD: Does anybody have any feedback on that one?

Markham Luke, MD, PhD: I think you mentioned short time. So FDA does put our PSGs out and we have a timeline to bring those PSGs after the new drug is approved. I think generic industry also should have a timeline for getting your product, your development plan together, even as you're waiting for the product specific guidance documents to come out. So I think that that timeline, you can look at it and say, OK, what things can I do to help

move that along before the pending deadlines for submitting your ANDA if you want to be first in line, et cetera.

William "Billy" Smith, PhD: Great. I guess, yeah, back to a summary of my rambling question was beyond the PSGs, there's obviously international standards, ASTM, ISO, there's methodology in manuscripts. And so this is kind of where, especially for kind of complex, novel complex products, a lot of that methodology or analytical capability is currently and maybe is not in an official guidance. And I just wonder what areas you guys think some of that research effort could be put towards. Go ahead, Andrew.

Andrew Cooper, PhD: Yeah, so I think, I don't think that in general we want PSGs to become more prescriptive, because as you said, it means they get out of date really, really easily, and I'm sure you don't like that. But I think one thing that's been really helpful in the past, and I'm thinking back to 2013-ish, 2012, 2013-ish, in my own area, where the current PSGs for OINDPs were kind of beginning to come out. And there was like a seminal publication, the Lee publication from Sau Lee, which we all referred to, because what it did was to provide the sort of underpinning of those PSGs. It helped us to kind of understand the agency thinking behind it. And what that meant is that as we then were approaching pre-dev meetings, we weren't trying to second guess agency thinking. We kind of already had some understanding of agency thinking and we could immediately start to work with the agency to work through what the PSG was actually requiring in terms of the methodologies. And so I think, I don't know how easy it is for papers like that to be produced, but that feels like it would fill a real gap. I mean, and to be honest, we're kind of in that position with OINDPs a bit at the moment, where we've seen a further evolution of the guidances. And okay, I know that you guys get out to conferences and that, but there is something special about a peer-reviewed publication with a long list of references that really helps to cement our understanding of where you're coming from. And I think that starts the dialogue around a specific product development on such a strong footing that I'd really encourage that to be happening.

Markham Luke, MD, PhD: There was actually a set of two papers, I believe, that we put in both from the bioequivalence and then from the quality perspective.

Andrew Cooper, PhD: Correct. Actually, yes, yes, you're right.

And the team that put it together is led by our folks in the audience, Brian Newman's team, as well as our OPQ folks. I think it's possible to do this for other areas, and we've done that to some extent, some of it from talking at meetings and putting out papers, and some of those are more piecemeal, but it sounds like you'd like to have one paper that consolidates a lot of that thinking.

Andrew Cooper, PhD: Yes, it's easier if you've got one place to go, I think. And I kind of actually, I remember now that those two papers actually work together pretty well. But I think if it gets too piecemeal and that gets a bit difficult to pick the pattern, it's really good if it's kind of quite consolidated.

Markham Luke, MD, PhD: Thank you for the compliment.

William "Billy" Smith, PhD: So I guess another thing that seemed to come up is as far as one, there's the clinical relevance of a CQA or a test methodology. And the next is applying that through some kind of risk assessment to develop specifications for the product. And there's also whether or not those methodologies are just being used for BE or translating all the way through to QC. So I wonder from the industry perspective, as we want to hear from you guys, kind of the quote unquote bio-relevance of, say, a test method or the actual implication of an in vitro method on product quality or efficacy. I just wonder where you think we're being not descriptive enough or whether or not things like different statistical comparisons, are there things that we can be doing? Like we have the draft guidance on budesonide that has the whole population bioequivalence math in it. Like whether or not those kind of things are helpful as a way to translate through from a one-time pivotal study to turning something into a QC method. And also Praveen, if you're online and have any input on that.

Praveen Chappa, PhD: We could see there are a lot of questions around this topic, meaning how our dissolution methods are linked to critical biopharmaceutical attributes. But again, from industry perspective, it is still person to person, what extent we do. Despite our expectation to have 80% release for particular products, it would be very difficult what is that parameter we need to target. You know, if you go with even lower RPMs and resolutions or lower volumes, it could be discriminative, but would not meet the release perspective. That's where I think in this perspective, we feel that there could be certain guidance around this topic. In the recent past, the deficiencies are enormous across the products and would be really helpful if we come up with certain strategy, like in Europe, in China, there are certain guidances a bit clear on you try this, this, this, and then see if it doesn't work and then justify scientifically, right? And possibly if we could have such kind of support, guidance would be really helpful and beneficial to the industry so that we can avoid several recurrent deficiencies on this topic.

William "Billy" Smith, PhD: Go ahead Clare.

Clare Butler, PhD: I might just add to that, and I agree with Andrew's point on not making PSGs so defined that we remove the flexibility and being able to move forward with science, et cetera. I think where we'd find it helpful without making it too prescriptive, and I'm

coming from the respiratory side, that's where my niche is, so I can speak to PMDIs and DPIs and soft mist. If we knew in the context of just dissolution method development and validation, it's more so with respect to what constitutes a respirable dose. What are the cutoffs that would be expected in an emitted dose sample? Not tying it to it has to be X or Y, but just those type of things have a very specific effect on the dissolution profile itself. So whether you use, say, a USP inlet port or an anatomical mouth throat, the respirable dose obtained from both of those methodologies creates a very different dissolution profile, and which one is more clinically relevant. I think they're just those things that just we, I think we could further align on without making it too prescriptive, if that makes sense.

Niraj Mehta, PhD: Quick comment. I think, and it was something that Praveen was saying a little bit too, just when we look at the resources and the information that you have from all the different discussions that you'll have in all these spaces, right? I think that anonymized, whether they're Q&As or whatever information that you can put out there. Again, via an anonymized kind of platform is really helpful to see because it might not be an apples to apples comparison. If you talk about dissolution studies, you talk about specific specs, whatever it might be, PSGs, all of those things kind of combined, right? So it's not about putting in more detail. It's about kind of saying, and again, to some of the other, and maybe this also goes to kind of a reliance question, right, of how you can look at whether it's guidances from other countries, what other organizations, and how they kind of lay out their expectations, right, and kind of put them in line, whether it's standard templates or whatever that might be. But again, providing that additional information of, here are some pitfalls that you might want to think about as you're going through, maybe even before you're going through your pivotal studies, right, whatever that looks like. So we're not going through this process of investing a lot of resources and then coming to you with the problems, right? So it's more of a general comment, but kind of piggybacking off of, it's not about kind of, for me, at least not specificity based off of where you're talking about your individual products, but kind of more general themes, right? And we talked a lot about that yesterday during the nitrosamines discussion as well.

William "Billy" Smith, PhD: OK. Yeah, so I guess in the interest of time, I would like to thank all the panelists, if we can thank the panelists one time. And I also need to tell you, if you have additional input, please use the online docket. And if you are one of the people who is here in person, there are feedback surveys on the tables. So please fill these out and drop them off at the front out there when you have a chance. I really want to thank everybody again for this interesting discussion. I know that this is kind of a pain point for a lot of people. And so looking at what specifically we can do to help minimize multiple review cycles and help kind of harmonize expectations between the FDA and what what we're asking of you guys as part of submissions is a really big part of our effort for the

GDUFA research priority of the funding. So I want to thank everybody again, and let's go to lunch.

Markham Luke, MD, PhD: I also want to encourage during lunch for folks to network, like people have come across the pond to visit us and so FDAers in the room, please be available for a networking opportunity with other folks, etc.

William "Billy" Smith, PhD: Thank you.