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Session 5 - Challenges and Opportunities for Modified Release Generic Products

Co-Moderators:
Dongmei Lu, PhD Associate Director, DTPII, CDER, FDA
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- **Considerations for Additional Strength Waivers of MR Products**
  James E. Polli, PhD Co-Director, CRCG and Prof., University of Maryland

- **Unlocking Strength Scaling for Extended-Release Tablet Development: Research Gaps and Opportunities**
  Jie Shen, PhD Associate Professor of Pharmaceutical Sciences, Northeastern University

- **Advancing Generic MR Product Development Using Tiny-TIMsg to Predict In Vivo Performance**
  Lieke van den Elsen, PhD Scientific Advisor, InnoGI Technologies

- **Criteria to Decide Whether pAUCs Are Appropriate BE Metrics and Alternatives When They Are Not**
  Charles E. DiLiberti, MS President, Montclair Bioequivalence Services, LLC

- **Opportunities and Challenges with IR/MR Dosage Forms in Lipid-Based Formulations**
  Karunakar (Karu) Sukuru, RPh, PhD Global VP, Pharma Product Development, Catalent Pharma Solutions

- **Quality Control of 3D Printed Controlled Release Dosage Forms in Distributed Manufacturing Networks**
  Stephen Hoag, PhD Professor, University of Maryland at Baltimore

Panel Discussion

In addition to moderators and presenters listed above:

FDA Panelists:
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Closing Session

Challenges and Opportunities Related to the Development of Generic Drugs

Anna Schwendeman, PhD Co-Director, CRCG and Prof., Univ. of Michigan

Closing Remarks

Robert Lionberger, PhD Director, ORS, OGD, CDER, FDA

Moderator: So good afternoon. I think not many people are back from lunch, but it's 1:01, so we'll get started. All right. So welcome back. It's my pleasure to kick off this afternoon session on the modified release products. In this session we are going to hear from the industry as well as academia. So we have 3 professors here in the panel. And so what we're going to hear are the challenges and the opportunities on several diverse topic areas related to modified release products. Such as the scientific considerations for waiver approaches of generics and that includes waivers of additional strength as well as the waivers of in vivo studies relying on complex in vitro and in silico models. And we will also hear challenges with the implementation of certain bioequivalence standards set by the FDA and then potential approaches to mitigate these challenges. So that's what our session for the MR is this afternoon.

I just also wanted to add here that the MR topic is also up for harmonization when M13 gets closer to completion and in this regard, FDA is also proactively considering research in areas especially where the bioequivalence recommendations between regulatory agencies are currently a little diverse. We kind of proactively started some research there. And the takeaways from the discussions in this session today will also be used to inform the research to support the harmonization of MR products. So I look forward to interesting presentations and of course the discussions following that.

So with that, maybe I'll invite our first speaker Dr. Polli. Yes. And Dr. Polli is a professor at the University of Maryland. And then he's also the Co-chair for the CRCG. Right. OK. Yeah. Thank you.

James Polli (University of Maryland): Thank you so much. Thanks for the invitation. I've really enjoyed the last day and a half. Hopefully this afternoon will be as good as the prior sessions, and again what I'd like to speak with you about is considerations for additional strength waivers of MR products. And I think I was asked to talk about this because maybe no one else would or could or something like that. OK.

So here are the topics I'd like to talk with you about. Is the term proportionately similar? There's some guidances that point to this. Some relatively recent guidances also talk about an example involving Concerta, a pellet product that's marketed. I think Jie's going to be talking about this shortly, but just the observation that you know slower release is expected from higher strength diffusion controlled matrices and then last month we actually conducted a questionnaire survey and very fortunately, some several folks in the generic industry who have a lot of experience with MR products kindly took that survey. And then just some suggestions about future research. OK.

So this is from the 2021 ANDA guidance talks has a term proportionately similar, which I think you're probably familiar with, but then of course it also says, you know, there's also open to other definitions of proportionately similar. Of course, I think that's kind of an open question, including related to future research perhaps. And then as you may know, M13B I think came out relatively recent, I guess in March. It's I remember it's at stage two or Step 2. It uses this term

directly proportional each strength containing the same ingredients in the same proportions. However, it does allow for other you know, deviations. I think it's a word it uses. In fact, there's an entire annex in this in this in M13B, which again is entirely about IR additional strength biowaivers.

It also kinda also mentions high potency drug products, those that were 5% or less of the IR product is the drug. And it says, you know, if if the only difference is the amount of drug, all the excipients are the same across strengths and including in same quantities. And that's that's proportional. Or if you swap out a filler in the drug so. So it has some some reasonable leniency there. And you know, it's a bit of a road map to read the guidance. Obviously it's a complex product about additional strength biowaiver for IR and then just I have just listed there some of the factors that are consideration dose proportionality in PK, drug solubility, formulation, proportionality similarity and dissolution, whether it's rapid or not high potency. And again there's also a section there about PK dose proportionality of drugs since again that's a factor. And from a generic point of view, that's often related into the reference product. So does is the reference product PK proportional, which presumably the generic has no control over.

So bracketing, of course, we're talking about lower most commonly lower strength biowaivers. Bracketing a sense of well, if you do the something upper and lower and try to get some things in between does say bracketing is needed when there's dissolution dissimilarity across strengths. Whether you know if there's deviations in direct proportionality of the core beyond the annex and when it's non dose proportional terms of PK. And it. And it does go on the guys to talk about, you know, what does it mean to be linear PK? And essentially it's basically probably what you already know in terms of mostly an emphasis I think on as I read it on a use on AUC being related to dose in a linear fashion more or less? OK.

Just so I thought it would maybe do one example of inspecting about proportionality with kind of an emphasis on formulation proportionality and PK proportionality is Carbatrol. It's around for quite a while. Carbamazepine capsules 100, 200, 300 milligrams strength. It's a beaded product now. The beads are somewhat complicated, but it's the same beads across all strength. They just differ in the number of beads. And in the label it actually says extended release Carbatrol is linear over the dosage range 200 to 800. The strengths are again are 100, 200 and 300. It says the epoxy metabolite is linear also in the label and even further goes on if you go to drugs at FDA that 2 by 300 milligram is bioequivalent to 3 by 200 milligrams. So that seems like it's a very nice strength that this is maybe a very straightforward type of product.

But having said that, there's always something. Maybe Carbatrol may as you may remember, is subject to auto induction on, you know in consecutive dosing, which of course the drug is taken multi dose and if you look hard enough, you'll find some articles that say the clearance is dose related. So you know what does that mean? Does that mean it's not dose linear even though the label says it does? So the point I'm trying to make is and again, this is presumably in the context of the reference product assessing whether or not a reasonably straightforward drug is dose linear or not. So that was that was the point about that.

Just maybe a second point. Again, I think Jie will play talk about this. Haven't seen her slides yet, but just sort of based on first principles for diffusion matrix type system. Something like HPMC, one of the more common approaches to formulate MR orally slower release can be expected to be expected from a higher strength from a diffusion control matrix. So if you have a

scenario where you get twice the dose by having twice the powder of the same powder that's bigger, physically bigger. It's a longer distance, so longer diffusional different. The distance here. So here we're looking at a sphere in terms of the radius. So to be a bigger sphere you need you need a little bigger radius and just to a first approximation, or if you get a for twice the distance, you're going to be about twice or squared, or four times the diffusional time. To a rough approximation. So you sort of pay a price for size when it comes to diffusion.

And then here's something from the literature. This goes back a couple years now. The product generic of Wellbutrin 300 milligrams. I think there's AI think the story is that it was approved based on a lower strength and as it turned out, when the FDA did a a bioequivalence study of the higher strength, they were well you can see the magnitude of difference there. Technically not bioequivalent and you know we we sort of so you can see how the blue curve, the higher strength curve is less than the reference curve and perhaps it's related to this this principle of diffusion and and and strength and size and that sort of thing.

Last thing I'd like to the main thing I'd like to maybe talk about is actually a survey that we completed just last month, a waiver of in vivo BE of lower strength products for proposed ANDA products that are oral modified release. Yeah, like I did this because there's really not much literature, particularly on this topic. There's a lot of formulation literature, of course, over the years, perhaps mostly in the HPMC area. But it doesn't always necessarily address this particular topic, and the questions that kind of come up in this topic. Like. So this was an anonymous survey and IRB approved survey. Really happy that there was really several dozen people that answered the question. In particular, there were, I think, people that we wanted to hear from. So the most common respondent was a scientist at a generic company that also develops innovator products, by the way, and the majority had over 10 years in the modified release or bioequivalence arena.

And is a little bit hard to read. So I think here there's there's essentially 6 factors that are listed here. I'll just read them to you and the way the survey worked is well, here's here's some factors and there's some desirable scenarios for each factor and undesirable relatively undesirable scenarios for each factor, and under which combination of conditions do you think it'd be OK to have a lower strength. This is lower strength biowaiver type of question so. And people were asked either yes or no. It'd be OK to have a lower strength biowaiver based on this set of factors. Whether the factors were good or bad, and the factors themselves were dose proportionality the reference across reference product strength. Again, something probably the generic company doesn't control. And by the way, there was three options. A person was was asked to consider the following like yes, it is proportional proportional in that it was either consistently bioavailability, cross strength, first time actually heard that concept was really from Rob Lionberger about a year ago, which is actually different from linear PK. That's probably something to discuss a little bit more on. And then also whether bracketing was in place.

So if it was bracketed then there would be like, yes, it's a good scenario. The alternative is that no, it's not dose proportional in any of those way. It's not consistent across bioavailability across strength. It's non linear PK and there's no bracketing in place, so it was one factor, another factor, same mechanism of release between test and reference. Again, we're asking the question, is it OK to have a biowaiver for lower strength test formulation and ANDA product? 3rd factor and 4th factor had to do with quality. Had to do with Q1 and Q2. You know, you kind of Q1Q2 or Q1 and Q similar or maybe just Q1 or or neither that was tied up in two questions. High, high experience of the test formulation research team in terms of technology dissolution.

Similarity across test and reference formulations across these strengths. And then also similarity of the test formulation across strengths.

So it's kind of funny that, you know, in some ways we think this is kind of a familiar topic in terms of formulation of, say, HPMC matrices. But then when you start looking at it this way, it becomes increasingly complex actually. And there's I think I think there's probably just not much research out there in a way. OK. So some of the assumptions with these scenarios were test and reference performance. Equivalent test has been demonstrated to be BE for the for the highest strength to the reference. And then there were four scenarios. A B C and D scenario A was very simple. All those factors that we just talked about were good for lack of a better term. Scenario B was where one and only one of those factors was no like bad. Everything else was good. Scenario C was very similar. Except the mechanism was no, it's not the same. But they weren't too different. And what was what was what was provided was that the tablet, like the the test, was a tablet, but involves modified release beads, unlike the reference. And then scenario D was the same as C. But you knew nothing about mechanism. You just knew the mechanics were of release were different. So it kind of went through this progressive stages of increasing differences from everything's OK, because that'd be my opinion. To increasingly more different.

And here's basically a summary of all the different results, and so you can see here on the left side is the like factor or the problem because in most scenarios there was something that was incongruent with ideal and this is the percent responded no or uncertain. So people can either say yes biowaiver's OK. No, biowaiver's not OK or I'm not sure. So larger numbers means less uncertainty. You know less, bigger numbers are sort of like, no, it's not good. So by the way, for the first scenario, all good. There was actually 13% of the people said either no or uncertain. And interestingly for the last, the very last scenario, there was 13% that said, yes, it was fine. So there's these two extremes of about 13% where? Yeah, no, it's not good no matter what. And yeah, it's good. Like, at least within the confines of of the of the survey.

Oh, OK. But if we if we can't just go through scenario a of scenario B here where the mechanism was the same. And you see a lot of red things here. So the majority of people, I guess the big observation is that it only took one thing not to be perfect for people to have doubts. So the biggest 180% said no or uncertain when dissolution similarity of test formulations across test strengths were not the same. But not too far behind that dissolution, similarity between test and reference, 71% said no or I'm not certain. Q things were not Q. One, there was a lot of uncertainty. Then again, everything else is the same, including same mechanism. And then dose proportionality of the reference across reference, you know, half the time people said I'm not so sure or no. And again, that's obviously not something that people control. And again, I would just refer back to what I said earlier in terms of you know what does it really mean or what's the relevance of dose linearity and I think Rob was right when he describes for the first time to me last year when he said, you know, isn't the real thing about consistent bioavailability across strength, as long as you give two of the one hundreds and get the same PK as the 200, isn't that what's important compared to, you know, it doesn't have first pass metabolism or whatever or non linear first pass metabolism.

And then in scenario C&D. The numbers just get smaller because we're adding more challenging situations. For example, in scenario C&D, we've we have different mechanisms. And in fact, well, for these first two, the only difference is different mechanism. Again, that kind

of went down to about 50%. If you have a different mechanism and that's the only thing half the people are saying. No, I'm I don't. I'm on nowhere uncertain. So that's that's kind of in a nutshell. What? So. So I'd say people are pretty conservative basically. But Admittingly that's it's a complicated problem.

And then here was supposed to be an easy question. And 95% said yes. So basically this was a beaded product. Where everything was was fine and I think my sense is people haven't really analyzed some of the comments yet, haven't had a chance to do that. But my sense is, you know, beaded products are kind of viewed as a little more simple formulations in the in the context of this question of lower strength biowaivers. So it's asking, do you agree that a waiver of BE for lower strength test products of this beaded product were the only difference is number of beads is appropriate 95% ninety 5% of respondents said yes to that.

So here was another question that was intended to be equally easy for like a better term, but dealing with HPMC based matrix. Where it's saying that you know, using the identical final blend strengths are obtained via only using different amounts of the final blend. Do agree that the waiver of in vivo BE for lower strength products is likely inappropriate or I would say yes. Again, you know because of the size and diffusion, all that sort of stuff and it was kind of split 58% versus 49 that doesn't really add up, OK. All right. Sorry, I did this all in one, but it was pretty close. And I I I think part of the reason and I haven't had any chance to look at all the explanations. I think part of his people are sort of saying, well, this is doable if you, you know, change the surface area to volume ratio, this sort of thing. So. So in a way, even though this kind of surprised me, this result, I do think it implies that there a lot of technological knowledge to compensate and and deal with this familiar problem. But of course the question is, how can that be done reliably right? Having said that, I would still say I'm kind of surprised at the results where definitely more than almost half the people indeed did did say no or uncertain to what I thought would be an easy question. OK.

So in a summary, there's a lot of people who are always, yes and always no and but. But as soon as one of the factors really was in in had some degree of question. There was a lot of people that were very conservative and said no, I don't think this is possible and in order they were again dissolution, similarity of tests across test strengths, dissolution, dissimilarity with cross test and reference. Not being Q1 not being dose proportional the reference and if there's different mechanisms. So that was the order of of pain, so to speak.

And as far as future research, yeah, I actually had some trouble assessing whether a drug was linear or not. I maybe others would find it harder. Found it very hard to find whether it was consistent bioavailability across strengths. And I I have a hunch that what Jie is going to be talking about it, that would be sort of my overall sense in terms of research focus taking the most important formulation approaches like HPMC matrices for example, and just having a good understanding of how those scale across strength and making sure there's tests that can be sensitive to when things are problematic. Thanks a lot.

Moderator: Yeah, thank you, Dr. Polli, for sharing your survey results with us. The next speaker is Dr. Jie Shen and Jie will be talking to us about the strength scaling for extended release tablets. Sorry. Yeah, she'll be talking about the strength scaling for the extended release tablets. That, and that's within the product line and she's going to share her research outcomes here for with us. Thank you.

Jie Shen (Northeastern University): Thank you so much for the introductions and I'm very happy to be here for the first time attending the public workshop in person and I really enjoy the workshop and all the interesting discussions and questions asked so far and also thanks to Dr. Polli to lay the ground for my presentation, so I'm going to briefly talk about extended release oral drug product specifically on tablet drug products. A couple of case study on HPMC based hydrophilic matrix tablet. Then we're going to spend the last one or two minutes to discuss research opportunities to start a presentation.

We look at the landscape of oral modified release drug product specifically on extended release drug products. So you can see we have different types of products in terms of capsules and suspensions and also tablets. So if we look closely, so we notice that a lot of these products have multiple strengths. So we think about the question is how we can scale our formulation for additional strengths and what are critical parameters we should consider when we develop generic drug products.

So obviously the dosage form design is very important when we have matrix versus reservoir type of drug products. So we typically have diffusion dissolution and also erosion involved drug release mechanism or combination of all the mechanism together. But we also have osmotic tablet which has semi permeable membrane and we also have diffusion and control the mechanism. If we take a close look at one type of matrix tablets, specifically hydrophilic HPMC based tablets. So you can notice what we have here is we have a swollen gel formation there and with the time we have erosion row and we have drug slowly get out and Dr. Polli mentioned earlier. When we think about the dosage form design. One of the parameters we can consider is not just the different types of dosage forms and polymers we use the drug to polymer. Also the geometry or two volume ratio are all very, very important for HPMC based drug tablets. So we have a combination of swelling and diffusion and also erosion control release mechanism.

Few example what we have existing drug products. So you notice we have some of them are very potent. So we have a small amount of drug API in tablets. But we also have some formulations with wide range of, for example, quite infamous. So we go from 50 mic to 400 mic. So we look at the existing PSG for those products. So you'll notice for most of them BE study is recommended based on the highest strength and obviously we have to consider dissolution performance similarity on the different pH conditions. And last but not least, for many drug products specifically PSG's approved or revised prior 2021. So you'll notice we have formulation proportional similarity listed there, and for recent revised PSGs we notice we talk more about the update to the FDA guidance, which was published in 2021.

So if we look at the FDA guidance and the EMA guidance side by side, you'll notice there are many similar parameters to consider in terms of same type of release mechanism or same manufacturing processes. So the one key difference between the FDA guidance and the EMA guidance which was published back in 2010, you probably noticed is the formulation proportional similarity or dissimilarity for the FDA guidance, as long as this is justified. So the formulation similarity does not have to be followed strictly.

So we want to give you a couple of case studies. So you look at different scenario. So the first case is on so both drugs are BCS, BCS Class 2 compounds. So it is a HPMC system. So the highest strength is 500 meg. So if when you look at the dissolution performance under different conditions, so the lower strength 250 has a almost similar based on F2 value, it's above 50. So similar dissolution performance as the highest strength. But when the company was developing

or using this product so they use the IVIVC based approach. So they noticed that even though the lower strand has similar performance as the higher strands, but based on IVIVC it's not bioequivalent. So what they did was they modified the formulation. They increase HPMC total amount and also they vary the surface to volume ratio. Eventually, that's the product or lower strength product that was marketed. So this is one example.

So next I'm going to show some of our recent research. This is again a BCS Class 2 compound, which is pretty autosoluble, so it has a pH dependent solubility profile and currently they are 5 strains is available on the market from 50 mic to 400 mic. I did highlight 200 mic because this is currently listed as a BIOS strength based on PSG and kind of follow up on what Dr. Polli discussed earlier. So for this particular compound and those unit, proportionality and linear were observed. So that's on the PK performance of the product. If we look at this product across the strengths, as you notice, the size variation is not as significant. So in terms of surface to volume ratio does not change that much and we want to understand what are critical quality attributes we can use or utilize to support strength scaling.

So we look at the matrix structure. This is X-ray micro CT. So we notice a similar microstructure on the dry state, so we notice the void space or density difference, and we look at the hardness. Hardness was very similar, so we want to also understand the dissolution performance across the strengths using different types of a media. So the first median, so you notice is a biphasic release method. So we start with pH 4.8 and going up to pH 6.6 so this is USP or FDA recommended method. And we also tested products across the strengths using biorelevant medium, both under fasted and fed conditions. So for the reference drug products across the strengths we observed a very similar dissolution performance in different types of media, I want to emphasize for the USP FDA recommended biphasic. So when the reference product was approved that there was a level, a IVIVC established for the highest strength 400 mixture. So we know this method potentially can have a biopredictive ability. So we look at all these.

So we want to understand matrix changes during dissolution. So we use the different types of imaging tools to look at the matrix changes. So based on the SDI two imaging, we can see very obvious gel formation over time and using X-ray imaging. So you notice that we observed porosity and swelling during dissolution. So all these are dry samples. So now we have all the information from the RLD products, so we really want to understand when we consider strength scaling, what are the key formulation strategies or in terms of critical quality attributes, what we should consider so we take closer look at the composition of the commercial products I want to emphasize. So this all the information obtained from public available sources. So the reason I highlighted the 300 mixed strengths, this is the strength we found the detailed composition information from a patent. So you notice that it is a HPMC controlled system. There are two types of HPMC was used to manufacturing this tablet, so it is a low viscosity K-100 LV and also a medium viscosity K4M. So these are the physical chemical properties of those two type of excipients.

So we based on patent information, we made our own formulations. So if we follow exactly the same formulation, so we also made two additional formulations that have different formulation compositions. This is just an imaging to show you the tablet, a representative one we made in the lab. So when we look at the dissolution performance of those formulations with either similar composition or different compositions, so you notice that even when we increase the total HPMC content from 30% to 40%, we still have a very similar dissolution performance based on again the biphasic method that was used to establish a level, a IVIVC. So based on if this

information we want to understand, what is the design space or safe space within which even though we can vary the formulation slightly, we can still have a similar dissolution performance.

So we conducted a DOE study. This is still part of the ongoing work, so we started with three micros formulation, so based on RLD study results. You can see within this entire zone we can have a similarity factor F2 value about 50 which indicate a similar dissolution performance using the biphasic medium method. So these are just few representative formulation I listed here for your reference. So you can see if we consider this is our center point about 30% total HPMC and 2.75. This is the ratio between K-100 and K4M. So when we either increase or decrease total HPMC amount and vary the ratio between those two HPMC polymers so we can achieve a similar dissolution performance as our own control or center point. So based on this information, if we consider 300 as our highest strength, if we want to develop a lower strength formulation that say in this case A200 formulation.

So similar study was conducted, so you notice that if we follow the proportional similarity in principle similar as what we observed for the RLD drug products across the strengths. So we keep the total HPMC amount as 30%. If we use the same same ratio, so we notice a very different dissolution performance. But when we change the total HPMC amount or the ratio of those two polymers, we were able to achieve a similar dissolution performance. Just to put the information together to help you look at in a different way. So you can see obviously, the release controlling polymer HPMC is very critical in terms of grade in terms of total amount and ratio. And across the strengths, if we follow exactly the same, sometimes we don't get similar dissolution performance. However, when we change the total HPMC amount, which means our formulation is not proportionally similar, we were able to achieve a similar dissolution profile. So as I mentioned earlier, we try to identify what are the critical factors when we scale up or sell scale down our formulations. So we look at, we try to explore different technologies and to see if we can use some new technologies to help us better understand the drug products.

So this is one of the things we looked into. So we use again, this is X-ray micro imaging. So we can do segmentation across a different region of the tablets in a non destructive way. So this is kind of like two very different drug products. So for our model drug products across the strengths we observed a similar microstructure, but for clarity in two different strengths. One is tablet in tablet, the other one is matrix. So we can observe very different performance. So one possible way we can quantify, but this is very initial data. Is to look into the true density distribution from center towards the edge of the formulation and we are also doing similar type of study on dissolution samples collected at different time points and try to see if this is potentially one of the parameters we can use to help us better understand product similarity and potentially support the approval or developing of additional strengths of the product.

Just to summarize, the key takeaways from my presentation I mentioned earlier, when we have a compositional dissimilar formulations as as we control the release rate controlling polymer in certain range, we can still have similar dissolution performance. Presumably this back to what Dr. Polli mentioned, we we have linear PK and also in terms of surface to volume ratio for this particular product that was very similar and I mentioned the importance of total HPMC amount and HPMC grade or ratio.

I want to spend the next few minutes focusing on what are the research opportunities or research questions to be answered. As I mentioned, we try to identify exactly what are critical quality attributes that we can use to help us or support the approval of additional strengthens to

help us scale the formulation up to higher strength or down to the lower strength in a reliable way and whether we can use some new imaging tools to help us better understand the structure of those formulations and use using those parameters to as more holistic approach for formulation scaling. But I also want to emphasize that I didn't cover this because I know our next presentation from InnoGI is going to talk about the food impact. So what are biopredictive dissolution testing methods we can utilize to help us better evaluate the performance? More of those more complex dosage forms under physiological conditions such as those ones with food impact. Because right now, for most modified release drug products, if we look at the PSG for equivalence studies, so you notice we request fed and fasted conditions at this for extended release drug products.

So whether we can use some or developing or validate biopredictive in vitro dissolution testing method that can help us better evaluate the drug product and whether those technologies can be incorporated in the guideline to support the approval of additional strengthens. Last but not least, so the two case studies I provided earlier. So you probably notice first of all, they are all HPMC based system and we have a relatively high drug amount in those products over 200 meg. But for some of the products I showed on that chart so we have very potent drug, very small amount. So whether we can develop a framework or road map app we can use the knowledge we gain from HPMC based system and expand or advance our understanding of how to scale formulations for other type of dosage form designs for example. Now we talk about hydrophilic matrix tablets, but we also have hydrophobic, or insoluble matrix tablets? We have film coated tablets, so all those questions or research areas are still to be understood and to be developed.

So with that, I would like to end my presentation by acknowledging all the hard work from my students. My post doc fellows, my team, and our collaborators from the FDA, InnoGI and Simulations Plus and the imaging analysis data provided by DGM. Last but not least, I want to thank the GDUFA research support and thank you everybody.

Moderator: Thank you, Dr. Shen, this was very nice, well thought through. And you had so many of the research recommendations for us. So thank you for that. Our next speaker is Dr. Lieke van den Elsen. She is the advisor, like a senior advisor at InnoGI Technologies, and over there she oversees multiple projects in the field of drug development. Then collaborating closely with customers in the pharmaceutical industry and she's going to be talking to us about on advancing generic product development using TinyTIM to predict the in vivo performance. Thank you.

Lieke van den Elsen: Thank you very much for the kind introduction and for the opportunity to speak here today. So InnoGI Technologies is a CRO with advanced models of the gastrointestinal tract. So today I would like to introduce you to the TIM technology platform and also show some case studies of the applications that the systems can be used for and also how the data can be used as input for in silico modelling as well.

So over the recent years, we have seen yet trends towards animal free drug development, including the really recent announcement of the FDA to even phase out animal testing even further. And I think this is a really great to hear and not only for ethical and sustainable reasons, but also because there is such poor correlations between animal models and humans. And this is clearly visible here in the image on the right hand side where the dots are literally scattered all over the place. So when we look at the correlation between dog models with human

bioavailability, the correlation is around 37%. So our odds of getting the right results are even better by just flipping a coin. And this is where we really hope that our TIM technology can have added value by providing really good correlations with human bioavailability.

And why is this so important? Especially for MR formulations. We all know that predicting in vivo behavior of these formulations is really challenging because it's not only dependent on the properties of the compound, but also the excipients and the interplay of the formulation with the dynamic conditions in the lumen as well as hydrodynamics etcetera. So the core of our technology are the TIM systems which are models for advanced drug release in dissolution and our main model is the TinyTIM system which models the stomach as well as the small intestine. In addition, we also have models for the large intestine called TIM-2. We also have Caco-2 model that is cultured under flow conditions with human-like mucus and human-like extracellular matrix to again provide a biorelevant model. More so than the traditional Caco-2 models and we like to use both this data from the models that I showed you also for in silico modeling where we use GastroPlus for our PBPK and PBBM modelling and this can result in good predictions of the pharmacokinetic response. So the talk today will be mostly focusing on the TinyTIM system, and I will also touch upon a little bit of the in silico work that can be done.

So the TinyTIM model is a very dynamic model and we mimic dynamically the secretion of all the gastrointestinal fluids. So this means that there is no media in the systems, but just the fluids as this would be in our body, we mimic the secretion of acids, electrolytes, enzymes, the bile pancreatin, etc. We also accurately mimic the peristaltic motility both in the stomach and the small intestine, and what I think is a really big advantage of the model is that we can use real food into the system, so we can literally cook up a meal and add this in the model. Then we also mimic the gastric emptying and pH profiles according to the physiological parameters and curves. And this is of course also dependent on the type of meal that would be used. And lastly, we mimic the absorption process by using a filtration system and this makes sure that the drug saturated fluids are removed from the system.

So here you see one of my colleagues adding a glass of water with a blue dye just for visibility into the stomach compartment of the TinyTIM system. Here it's good to mention that we can add also different type of meals here. So any type of food is possible. You see that the stomach has the J shape according to the physiology in our body and the different compartments are squeezing and mixing in different patterns to mimic the peristaltic. Then you see small amounts of the blue liquid moving to the small intestine, which is the horizontal compartment, and this is mimicking the gradual emptying process of the stomach on the right hand side is to filter units, and those samples are collected automatically from the system. Here we see that we can take samples directly from the lumen. This can be done both in the stomach as well as the small intestine and these type of samples can be taken at different time points to get a good understanding of both the dissolved and the total concentration of the compound of interest in the experiment. And this is the simple tray where automatically the filter samples are collected.

So that is in a nutshell what the TinyTIM system look like. So the type of data that we obtain from the models is usually the bioaccessibility profile. So in the TIM system, we mimic the digestion. So both the food as well as the dosage form are digested, which can be very important. For example, for the lipid based formulations that we heard a lot about this morning. Samples can then be taken directly from the lumen, but we also have those filtrate samples where we obtain the bioaccessibility measurement. And this is the fraction of the compound that is available for absorption through the gut wall. And it's good to mention that this is different from

the bioavailability. So if we want to calculate this, we utilize the PBPK modeling to translate this. But typically the bioaccessibility and bioavailability have a good correlation.

This is what the data looks like. So the top we see the lumen concentrations in stomach and the small intestine and from the filtrate samples we get the bioaccessibility profile and combining all these samples together we can calculate a dissolution profile as well. So today I would like to highlight a few few applications of the TinyTIM system that can be very valuable for generic MR product development, such as the interaction with food as Dr. Shen mentioned just earlier as well and also the co-administration with proton pump inhibitors. And as all the protocols for the systems are computer driven, we can mimic certain disease and age populations as well. So I will also show a case study for the pediatric population.

So this is just to give you a bit of an overview what we can do to mimic the pediatric patient in this study, paracetamol syrup was tested with different age relevant food matrices in the TinyTIM system. You see the three different age groups that we decided to mimic different age ranges, body weight and also the different food matrices that were used. So the age groups were chosen dependent on the maturation and the type of food consumed. And here you see the different parameters that we are mimicking with those different protocols. So the gastric volume is increasing with the age of the infants or children. Also the size of the meal is increasing and good to mention is that infants are feeding very regularly. That's why we also added a second meal into the system. After three hours. The gastric emptying is mimicked and also very important is the gastric pH, which is much higher in older children than in adults. And the intestinal secretions are also adjusted for the age. So using these three different protocols we tested the paracetamol solution and we observed that the total bioaccessibility was similar for all three age groups. So this was about 85% of the dose, but what we see is that the profile is different for the different age age groups. So the Tmax of the toddler was delayed compared to the younger children. And when we compare this with in vivo data we see that this matches the clinical observations. So in the neonatal Tmax was around 67.0 minutes, 66 for the infants. So that matches with what we found in the TinyTIM system, and this delay in the toddler was also observed with 114 minutes in clinic. So this is just an illustration how TinyTIM can be used for different pediatric age groups and it's predictive. We have used this also for different age groups and this is maybe a topic that might be worthwhile harmonizing on altogether. What would be the relevant age groups to study?

Then I would like to highlight the co-administration of acid reducing agents in the TinyTIM system. So in this publication, 12 compounds were tested, mostly were basic compounds, but there were also several salt forms. As these are traditionally more difficult to predict. And the compounds were tested either in the fasted state with a glass of water where the pH would then drop from three to 1.5 in 30 minutes, or with just a glass of water at a neutral pH and no acid secretion. So here you see the compounds that were tested in this paper and in orange is the three that I will zoom into in a little bit more detail. So two of them had a negative effect of the co-administration with acid reducing agents. And there was also one that did not show an effect.

So here on the left hand side for dasatinib, we clearly see that the cumulative bioaccessibility is lower with the increased pH in the stomach compared to the fasted state. And when we calculate the ratio of with and without acid reducing agent for the TinyTIM bioaccessibility we get a ratio of 0.4 and for clinical studies with the area under the curve, we get a similar ratio. When we look at erlotinib, TinyTIM did not observe any difference for the co-administration with acid reducing agents and this was also matched with the clinical studies. Looking at atazanavir, we

saw that there was a small effect of the combination with acid reducing agents and also in clinical studies an effect was found. But the extent of this effect was larger in the clinic. And looking into more detail why this might be the case. This compound is a P-gp inducer and inhibitor and it's good to mention that the TinyTIM system is not able to mimic those transporter mechanisms as there is no cells in the system. But overall, TIM was very successful in predicting the effect of co-dosing with the acid reducing agents on the oral absorption. So for all 12 compounds, the predictions match the in vivo performance for eight out of the 12 drugs, there was a high predictivity. And for four out of 12, there was a moderate predictivity. This can be seen in the image down here. And indeed, for this compounds with the moderate predictivity, the transport is an intestinal metabolism might contribute to these differences observed.

Then I would also like to highlight the use of the TinyTIM system as a biorelevance and biopredictive tool for food effect assessment. So in the recent paper, 20 compounds covering all BCS classes were tested and also all different type of drugs and different formulations. The test conditions were either in the fasted state with a high fat meal or a low fat meal. And the images here show that clearly the emptying of the stomach so shown in the blue is the gastric emptying and also the pH curves in orange are very different when we compare the fasted state versus the high fat meal. So This is why it's so important to mimic these conditions accurately. Besides that, the food ingestion can also change secretion of digestive enzymes, bile motility and viscosity. So all these conditions are mimicked in the TinyTIM system.

And here is an illustration. We see the bioaccessibility profile for a fasted versus fed state run. So the TinyTIM system I was able to predict for 18 out of the 20 compounds, the food effect ratio that was found in humans in this study. So you also see 2 blue dots here, which are for atenolol and metformin, and in this case TinyTIM did not predict a food effect for these compounds, whereas a small negative food effect was observed in the clinic. And I will come back to metformin in the next slide. Because once again, here, transport mechanisms are involved. And I'll show you how we can overcome this. But it's good to conclude here that TinyTIM can successfully capture the effect of food on oral absorption when it is related to the physical, physical, chemical properties of the drug or the gastrointestinal physiology.

So for metformin in vivo, absorption involved multiple transporters and as mentioned this is not mimicked in the system itself. But when we combine the lumen and bioaccessible fractions into a dissolution profile, we can import this into GastroPlus and we achieved here strong predictions of the human PK profile and also the negative food effect is clearly observed. So the Cmax and Tmax were in a good agreement with the in vivo data. So this is to illustrate and that's combining the TinyTIM system and output within silicon model modeling can really be a very strong. Yeah, a powerful tool.

So predicting the in vivo behaviour of modified release formulation in silico has a recent well up to now, quite often quite low confidence. So that's why we think this type of data can be helpful to improve the predictions and to assess the equivalence. And this also touches upon the work that Dr. Shen just described, where we can use TIM for testing of the extremes of the physiological and formulation parameters. A few of these are listed here and we have discussed or touched upon some of them already, and this can then be used in the PBBM population simulations to define the dissolution safe space for these complex formulations. And that is the work we are working on together with Dr. Shen.

So to summarize, the the TIM technology platform really closely mimics the complexity of the gastrointestinal tract and can provide strong predictions of the lumen conditions as well as the human bioavailability. Also in combination with food, proton pump inhibitors and for specific populations. And this allows for to establish bioequivalence between different strengths and doses form forms and to improve also the in silico predictions using data from the TIM studies.

So as also already touched upon by Dr. Shen, it is important that we define the critical parameters for additional strength biowaivers for these MR products and that is part of the grant that we are working on. We think that TIM studies could also potentially replace other clinical equivalence studies in certain circumstances and examples could be the BCS based biowaivers especially for BCS Class 2. The TIM systems have very good predictivity. And also small changes to formulations can potentially be studied in the TIM systems and of course the case by case biowaivers. For example, for the food effect and the proton pump inhibitor effect are of interest as well as pediatric biowaivers where it can be very challenging and unethical to test this in infants. And we didn't discuss this in the presentation, but also for locally acting APIs, the TIM system might be very interesting because we can look in the lumen itself and obtain samples from there, which is very hard to achieve with other models.

We also think that guidance could be helpful to harmonize the use of advanced dissolution methods for those cases mentioned and an example is also the pediatric population where it would be good if we can define the age ranges and the specific food matrices that are of interest to test so that we can harmonize this type of research. And then lastly, it's good to mention that using the TinyTIM system which is mimicking the upper GI tract, we cannot cover the full extent of the gastrointestinal tract and especially for extended release formulations, it might be of added value to also look at other solutions, for example including the colon model, the TIM-2 model to evaluate those type of formulations in even more detail. And I would like to leave it at that. So thank you very much for your attention and looking forward to the discussion.

Moderator: Thank you, Dr. Lieke. And our next speaker is Mr. Charles DiLiberti. He's the president of Montclair Bioequivalence Services and Charlie has about 40 years of experience in pharmaceutical industry and he's going to talk to us about his thoughts on partial AUC and what FDA could be considering a little differently from what what we're doing at at this time. So, Charlie, thank you. Thank you and thank you to the organizers for inviting me.

Charles DiLiberti (Montclair Bioequivalence Services): I would say a lot differently. All right, I prepared a financial disclosure slide. I found out later I didn't need it. So you get this one for free. I won't charge you. Legal disclaimer. If you have any thoughts of using the content of my talk for any purposes, first you must read this. But I'm not going to read through it now.

So what's the motivation for requiring partial AUC? Partial area under the curve, the plasma concentration time curve metrics for bioequivalence in the first place. For systemically acting drug products, there are cases where Cmax and the total area under the curve may not always ensure comparable clinical effect over time. And broadly speaking, there are cases, particularly with complex PK profiles where we would want a similar PK profile shape. Typically this happens with drugs that have a strong direct PK-PD link.

In contrast, the other broad category of using partial AUC metrics is for locally acting gastrointestinal drugs, which typically act at the the far end of the GI Tract, and drug concentrations may not directly reflect concentrations at the site of action. There may be a complex relationship, sometimes it even inverse where higher PK response may mean lower

drug concentrations at the site of action. Like if you deliver the drug too early, you might not have any drug leftover by the time the dosage units gets to the side of action. And the goal here is to ensure similar timing of drug delivery along the GI tract.

So there are very different objectives here. I'm going to focus almost my entire talk on the systemically acting drug products and only touch very briefly on the locally acting ones. So partial AUC criteria originally were applied to oral modified release, typically mixed mode where the the the formulation is partly immediate release, partly extended release formulations and later it was applied to inhalation products. Long acting injectables abused deterrent formulations and a few transdermal products.

In many cases, the partial AUC is expected to control one or more of the following time to onset of clinical effect. Time to offset or the cessation of the clinical effect, the duration of the clinical effect or in some cases to ensure that you have the same or similar plasma concentration profiles at certain time points post dose.

Quick reminder, total AUC AUC zero to Infinity is actually a good measure of the amount of drug absorbed. However, partial AUC is not. So you can see it from this plot here. This is a PK profile for methylphenidate and the FDA guidance specifies a area under the curve from zero to three hours. Partial AUC from three to seven hours and partial AUC from 7:00 to 12:00 hours. And it's pretty clear that the partial AUC from 7:00 to 12:00 hours is in the elimination part of the curve. Where very little, if any, drug is being absorbed, and yet it has quite a lot of area which represents drug absorbed earlier. So partial AUC is a notch or two below the utility of total AUC because it does not represent the amount of drug absorbed.

Now partial AUC represents the average concentration over its defined time interval. So if you have a partial AUC from time A to time B. And if you divide that by the width of the time interval b - a, you end up with the average concentration over that interval. And this is not pharmacokinetics. This is calculus, OK. You have a function plasma concentration versus time. AUC is the integral of that function divided by the width of that integral, and that gives you the average value of that function. So in real terms, let's take AUC from three hours to seven hours. The width of that interval is 4 hours, so you take AUC three to seven hours divided by 4, and that's the average concentration over that three to seven hour interval.

Now, because this is an average concentration, how do we calculate this average concentration? Well, if you go through the math of the linear trapezoidal rule, you'll find that the average concentration here is actually a weighted average of the individual time points that comprise that that make up that time interval. For example, if for the three to seven hour time interval you take plasma samples at 3, 4, 5, 6 and seven hours. The average concentration, and therefore the partial AUC is just a weighted average of those, you know, three hour, 4 hour, 5 hour, six hour, 7 hour concentrations.

Problems with the partial AUC metric. Well, the fundamental problem here is if your goal is to control when a particular thing happens. In other words, the time dimension as I showed in the last slide, the partial AUC controls the concentration dimension. It's the wrong dimension. We're measuring the wrong thing. So a second problem is that those individual time points that make up the partial AUC are often very divergent values. And when you take the average of a wide range of values that the importance of that mean value, that average value is diminished.

Imagine for a moment, take off your shoes and socks. Stick one foot in a bucket of ice cold water, one foot in a bucket of hot coffee. Do you really care what the average temperature is? Probably not. It doesn't make any difference. Similarly, with some of these partial AUCs which are calculated from very divergent values. Now a large reason for why they're very divergent is sometimes they're calculated over very steep sloped concentration rise or fall at the beginning or end of a PK curve, and in many cases they include sub therapeutic concentrations.

So my question is, if you're calculating a weighted average from concentrations that have a wide range of values that are steeply sloped and include sub therapeutic values. How clinically meaningful is that average concentration? OK. Partial AUCs also have questionable clinical relevance because they may be very highly variable or they may have a lot of variability from lot to lot of the reference product. Even though the intra subject CV may be low. And in some cases they are a poor there's a poor time choice choice of the time intervals for some partial mid AUCs, and by the way, just to put this in perspective. Industry, in my experience, hates partial AUCs. It's not like they get all excited and joyful when they see another product specific guidance come out with partial AUC criteria. OK.

So here are two real PK curves that have very different partial AUCs. And yet they probably represent very similar time to onset of action. Conversely, here are two PK curves with nearly identical partial AUCs, and yet the one easily achieves therapeutically effective values and the other one may never achieve therapeutically effective values, at least not over this interval.

So within a PK profile, if you do a linear regression over the concentrations that are used to calculate the partial AUC, some of these have very steep slopes and they have a lot of variability between the individual time points. So in this case, if you calculate the within profile CV. And then pool the CVs across all the samples, all the subjects in the study. The pooled CV is 63%. This is a lot of variability that you're calculating a mean from. Umm. Similarly, the slope of this rise time in in the early AUC is very steep relative to the average that you're calculating. So again, what's the clinical meaning of an average concentration under these circumstances?

So a middle AUC again. This is methylphenidate. It has three AUCs defined in the in the product specific guidance, the middle AUC. Maybe I'm wrong, but I get the sense that the middle AUC was sort of what was leftover after a decision was made that early AUC might sort of kind of represent the time to onset and late AUC might represent time to offset and middle AUC seems to me to be what was leftover because I mean the middle AUC here is sloped very sharply upward. And again, what's the meaning of an average when it's steeply sloped like that? Here this shows that you can have two PK curves where that middle AUC calculated. The GMR here is very close to 100% and yet these curves are very very different.

What partial AUC performance characteristics are essential? What should we demand? What performance characteristics should we demand of partial AUC? They should have low to moderate intra subject CVs. They should have consistent results across different lots of reference product. They should. The concentrations over the time interval defining the partial AUC metric should not be highly variable, not steeply sloped, and include few or no sub therapeutic concentrations. They should not be over too narrow a time interval, otherwise it's going to get unstable. They should represent a clinically or detect a clinically meaningful difference, not just differences for the sake of differences, they should include only a time frame where reference products concentrations are very high and therapeutically effective, and we should allow for interpolation, if you didn't do your study at those specific time points.

Products where systemically acting products where partial AUC metrics do make sense, or where we're trying to compare average drug concentrations within clinically important time intervals. In other words, the middle part of the PK profile, where concentrations are stable and flat like long acting injectables, transdermal patches, the middle part of the profile. Fine, let's do. Let's pick those time points where we have a flat portion of the curve where it's not sloped up. PK concentrations are not varying enormously, and I think that's all I have to say and we have to do this work quickly because harmonization is imminent on M13.

So there's some references here and I want to thank everyone.

Moderator: Charlie, thank you for sharing your perspectives and you given FDA some thinking to kind of take back for us. All right, so the our next speaker is Dr. Karunakar Sukuru. He is the global vice president at Pharma product development and Head science advisory at the Catalent Pharma Solutions. Dr. Sukuru also has over three decades of experience. Experience in drug product, the product development and technology, and he's going to talk to us about the opportunities and challenges with IR/MR lipid based formulation. So we're coming back again to the lipid based formulations, but it's important for us to hear. So thank you.

Karunakar Sukuru (Catalent): Thank you Nilufer for that introduction and first of all, I would like to thank FDA, the organizers for inviting me to speak at this event and special thanks to Dr. Dongmei whose regular feedback on during the prep time actually helped me to improve the content of what you would see today. I would also like to thank all of my colleagues at Catalent who helped in preparing this content. And also number of discussions that I had. I also want to thank all the previous speakers as they have set the stage very well for me, especially the morning session where there was a lot of discussion around lipid based formulations and the in vitro and in vivo correlation and food effect that makes my job easy. And I also want to say good, good afternoon or good evening, especially for almost 175 folks online. Wherever you are. Thank you very much for staying online and for contributing to this session.

So with that, I would like, even though this is an MR session, but the fact that they're not that many MR products approved with lipids, we also see from our experience there a lot of similarities between the two when it comes to the food effect and the in vivo in vitro challenges we see for both IR and MR formulations. Therefore, we try to cover both. So there's a lot of content here. My slides look busy, but I would like to make sure that focus just on the take home message from each slide and I understand these slides are made available to everyone, so don't don't get confused with all this content here. The way the outline of my presentation is, I will talk briefly about an introduction on the lipid base formulations. And the classification, which is my entire presentation, is based on my very first slide that you would see and some new developments that you would expect to see hopefully in in the future years with some of these modified release versions that are being worked currently and also there will be a brief review of formulation and process and analytical challenges.

We talked with some case studies and a brief review of food affect and IVIVC and conclusions, followed by what we think FDA need to help with improving the IVIVC current guideline to make it applicable for lipid based formulations. So with that said. This slide is very busy, but again the take home message is lipid based formulations. It's a very versatile formulation platform. And based on the physical chemical characteristics of the API, one can select the type of formulation that you want to utilize, whether it is type 1, 2, 3, 4 or 5B. And I also have a classification of solution versus you know the SEDDS and SMEDDS or SNEDDS and the non oil micellar

systems as well there with some of the approved product examples at the very bottom there. Also I want to highlight that even though this talks about lipid base formulations, the fact that over 70 RX products that have been approved over the last almost 70 or 80 years, all the way going back to 1941 with the Drisdol, the first product that was approved to current. Almost 65 of those have come from Catalent, and also I can say that the link here why I mentioned that is all of them are pretty much in softgels barring I think 2 products that are in liquid fill hard shell capsule. So any discussion about lipid based formulation can be complete without talking about softgels. So they go hand in hand when we talk about formulation or analytical challenges, we need to understand that there is also a softgel technology involved to make it a little bit more complicated.

But if you do a systematic development, that should not prevent one from developing these successfully, and to make that point. As you see on this slide, there are quite a few examples. The very first one is an extended release product, which is a calcifediol that was approved in 2016 by FDA and this is in a suspension based extended release formulation. So there are also a couple of other products I particularly highlighted. These are just to show that the versatility of this platform, that's not just solutions or SMEDDS? There are also suspension based formulations that really benefit from the lipid digestion or lipolysis that occurs to deliver these difficult to dissolve drugs. And also the other thing that you should note on this slide is a delayed release product. That is all the way to the bottom right side and also the various BCS class of drugs that have been incorporated.

So let me give a brief intro about doing some of the opportunities and challenges with MR/ER formulation with lipid based formulations. The challenge is to get an extended release formulation. You need to have a matrix that is very highly viscous, whether it is lipid only or whether it is combination of lipid or hydrophilic matrix. So this particular shell which is non gelatin based or carrageenan shell. This is the product that was approved in 2016 by FDA allows to work at a much higher temperature than your typical gelatin soft gel, which only can go all the way up to 35 to 40 at best. So that higher temperature provided the API is stable would allow or facilitate the encapsulation of precise doses in. In this particular example, this is a very small tiny capsule and successfully encapsulated using this technology.

So let's now talk about the various types of extended release fill matrices that are possible with the soft gel or even liquid fillers. This could be a combination of lipid with cellulose matrix or lipid by itself, or a combination of hydrophilic HPMC or polyethylene oxide type systems and the last one at the bottom right is about a combination of any of the other three along with the delayed release shell which is another version of, you know, modified release dosage form.

This slide is busy again. Just the only take home message from this is even if you're working with lipid based formulation combination with with cellulose matrices or say HPMC the particles, I still place a critical role as you could see dissimilar dissolution with HPMC particle size less than 63 micron versus greater than 63 micron. I mean, it could go up to 200 or 250, but within the encapsulatable particle size that we are talking about and they could influence the performance of the product now quickly.

I would like to talk about the delayed release softgel. As I said, FDA approved the first product with this valproic acid called commercial product name DEPAKENE in 2008. This a combination of gelatin with acrylate polymer single step manufacturing process. Then the second one was delayed release coated soft gel called EPANED in 2014. And the latest development is gelatin

with pectin. It's a single step manufacturing process where you see a coated versus OptiGel DR on the left side in the pictures and the table there. So again, it's something that you would see more and more hopefully in the coming years as we are working with different RX products using this particular technology testing and dissolution for these products. Again, I would not just rely on the pharmacopeial methods. For example this product easily met the criteria with EP/USP, but the criticality is to test this in a biorelevant media. And that's what we did. This slide shows that aspect successfully. That to prove the robustness of the product, it has been tested in multiple different media successfully.

Just there's a lot on this slide and the next slide as well. But what are the key formulation in manufacturing challenges you could see. Read it for yourself. But what I want to highlight, it's no different than any other generic formulation that you want to develop. I mean, look for all the critical attributes. In this case, the added challenges to check for both fill and shell, not just that means you know the compatibility between the shell and fill components. Any crystallization or oxidation potential solubility and precipitation. And also the stability of the emulsion, etcetera, those are all very critical.

Now this this slide again, formulation strategy, I don't need to tell anyone here. Everyone will know our RLD analysis and again in this case quite extensive testing is required to make sure that you identify the right type of gelatin using isoelectric point determination and GPC chromatography to identify the type of gelatin and the quantity and quality of plasticizers used. And also the shell fill compatibility. And the final optimization.

Now let's quickly talk about some of the analytical challenges. And again, I want to clarify that I mean, you know, there's a lot of buzz around that it's very difficult to develop analytical methods for lipid based formulation and no question there are more challenging and complex methods, but they're all developable and those who know analytical stuff, they will figure out, let's say compounds with no little or no UV chromophores or use other methods. Load those API excipients that interfere with UV detection and complex lipid matrices for all of them there are solutions. Only thing you need to look and address those the other point I want to make on this slide left side is the developing a discriminatory dissolution method is super important and FDA talks about this all the time and in fact the most number of questions that I've seen come for branded product development is actually related to dissolution, or at least one of those most important one and for this understanding of the chemical and physical chemical interactions between the fill and shell is very critical.

So now let's look at some case studies, cross linking enzyme and surfactant addition. So Tier 2 method allows when there is a cross linking for reversible cross linking. But the key here is for most lipid based formulations, surfactant is part of the dissolution media and when you add that surfactant can make a big impact on the effectiveness of the enzyme and also the type of enzyme. For example, in this particular case, study this particular molecule, the they recommended enzyme from USP is pepsin and bromelin, which underperformed the Blue Line and the Yellow line that if you can see here versus the Orange Line, which is pepsin. So again, the take home message is to identify the critical conditions as well as identifying what is the right enzymatic media for your particular molecule. And you can justify that with the data.

So another discriminative dissolution method example. Here we actually made the OptiGel DR slash the delayed release capsules that I talked about at the beginning, which made them with

two different 50% less polymer. The low polymer is 50% less polymer, but with the standard EP and USP method, there was no difference between the standard polymer versus the low polymer. They both performed equally well interestingly, but when we added pepsin to differentiate, we certainly see the low polymer breaking apart within the 1st 10 minutes to 15 minutes. So again, the need and importance of the discriminatory dissolution method, whether it is IR or ER dosage form this one is a very interesting example.

What we have noticed is a lipid based suspension formulation. I don't want to name that molecule here for confidential reasons, but at the end of three months, room temperature product actually failed to meet the dissolution criteria, whereas the 40/75 met. I mean, I'm sure you guessed it. I obviously you know at 40/75 the lipid matrix is much dilute or kind of in the melted state. But how do you address this type of a problem then what we realized is we actually manufactured this particular batch to address a content uniformity issue at a much at a different temperature where it formed a very strong solid matrix. So identifying the critical processing temperatures for liquid based molecules to ensure that you are getting an ideal matrix is critical. That's what this this is pointing to.

So now jumping to the next case study, we tested the the same delayed release capsules. We manufactured 4 different formulations and tested them with the standard EP/USP method. The very top right panel here on this slide. No differentiation. All are good, great. But if I have to pick one for BE study, I'm confused now. How do I pick out of the four? So what we did is we leveraged Dynamic Gastric Model DGM which to predict its performance. What is the best before we took it into animal study? Clearly we saw that in the fasted and fed state which this system actually is, mimics the entire GI tract and fasted and fed state. Based on this, we selected and the one that performed very good. The blue line in this graph, right the red and blue blue performed and met the enteric or delayed release criteria quite well. Reducing the burden of, you know, failures in the BE study. If not for this DGM we we would have had a difficult time or would have tested a lot more number of lots.

So now jumping too quickly the IVIVC why is it challenging for lipid based formulation there? A lot on this slide. I'll break it down for you to make it easy. The top panel is what are the challenges? I mean we cannot replicate what happens in the GI. Physiologically, with the changing dynamic process pH shifts, bile salts and all that bile flow you could mimic to certain extent, but you can't mimic the food effect really well. For example, you give a product with gastric emptying time. What happens in the fed versus fasted that that's a challenge there that he very hard to mimic and even from the TIM tiny TIM presentation, I notice that only eight of the 12 products it was able to predict quite well. So maybe that 20%. Are four of those products. Could fall into this category probably and then translating the animal validated models into human GI is algorithms. Challenging.

So now let's look at the second panel here this table. The good news here? The take home message is for SMEDDS formulation. Quite few of them actually had a good strong IVIVC correlation here and the references are listed at the bottom and I think. Sivacharan earlier presented this is his publication. Excellent presentation. There and then the bottom one, if you see, I want to highlight two products here, here and sin here as in both performed in vitro that you could differentiate, but when they went into in vivo study, they performed equally well, meaning both formulations the ASD or the crystalline version. Was no different in vivo and for a variety of reasons, and we don't have time to discuss here. But what I want to be careful. Or draw conclusion from this is. Just. Because it worked. For some it doesn't work and also I want

to highlight on this slide is the fenofibrate as a SMEDDS formulation met the IVIVC criteria, but whereas when it comes to suspension. It did not. So suspension in lipids. Definitely throws an additional challenge for generic development, just to keep in mind and on the next slide I'll talk about briefly the ER capsules.

We talked Rayaldi, so irrespective of the food labeling. It's expected that these products need to be tested both in fasted and fed state. Earlier, speakers talked about this and also the dose dumping risk has to be evaluated thoroughly. Now for food effect and implications for the generic development. If you see there are a list of just only three products. So if you see the drug product label says take with food. But the BE study requires both fasted and fed, which is also the ICH guideline talks about that. I think previous speakers spent a lot of time discussing that. I would only highlight that at the bottom panel there are some tests that that we think could help guide at least rank order the formulations by evaluating the solubility and precipitation by relevant media et cetera.

So jumping to the next slide. So this is a very busy slide. Again, my apologies, but very valuable information here on this. A generic version for Neoral was successfully developed and in vitro. You see, there is no difference in the dissolution and PK data in the dog between the Neoral versus the generic version. This, published from Seoul University. I think no difference, but with the version there is a clear difference and the same thing you see in the correlation. Great correlation for the Neoral SMEDDS. But what's the take home? Message from this the reality is in the human data there is 13 in vivo studies. Meta analysis was published in the second reference listed there points out that based on the age, body weight and the disease state and the type of organ transplant, huge variability within the Neoral to Neoral lot to lot Sandimmune to Sandimmune lot. So we need to keep those in mind and also Gengraf which is a bit of generic. As 39% organ. Transplant reject versus 25% for Neoral. What's the take home message IVIVC. We have to be careful for seeking waiver as an example for narrow therapeutic index drugs. This is not that simple. We need to factor what the therapeutic consequences are from a biowaiver for products like this.

So key take home message. Lipid based IR/MR formulations are very versatile, applicable for all classes of drugs. Including BCS, one assuming if it is potent, you know nothing better than putting into a solution of suspension. And also it is emerging as a promising technology again. I mean, I say this. I'm cautious. We're only at phase one or phase three level, at least for target protein degraders at this point and potentially for macromolecules and understanding of formulation. Fill, shell and analytical and process related challenges and food effect is key for successful generic development. Of lipid based formulations, whether IR or ER. And also there's a need for better IVIVC predictive tools for formulations, so.

With that, uh, proposed research areas for IVIVC in lipid based formulation. There's a lot on this slide just to focus on the headlines there. The current IVIVC guideline treats lipid based formulation and the excipients and what they undergo. Same as non lipid based excipient systems. That is where I think we need help and focus from FDA to support additional research, to quantify and to predict, develop better in vitro. In vivo models, lipolysis permeability and microsomal metabolism, I paid attention to earlier speakers presentation. Their tiny TIM could predict a lot of things. It's a great, great tool as. But the metabolism part is the missing part in that. So, right, those those are the type of things simulating GI conditions addressing any. The GI conditions during these model development is critical to simulate the all the changes that occur enzymes, bile salts, transit times, gastric retention from fed state, and also address any

limitations associated with the number of new tools like TinyTIM or DGM or GastroPlus software and Stella and few. Other software, all of them are great tools emerging, but there's more that need to be done to address the gaps in those. And studying the impact of food and linking that to. PBPK modeling right now, it's very difficult to link that to PBPK because the drug in the oil globules, even if it is soluble, unlike in the other ASD formulations, it's not available each each of those globule will act as a vesicle or a chamber. That is where the. Challenge for PBPK comes define the dissolution meaning again based on whether it is a solution or a suspension or an narrow. Therapeutic index drugs will need to. Identify. What? What is the appropriate way? And then last point, revising IVIVC guidelines for lipid based formulations based on the above. Points O. With that, I would conclude my presentation. I hope I got two more minutes, but wow. Thank you.

So with that, again, I want to thank the organizers and all of my colleagues at Catalent since I don't have a separate slide for that. We removed reduced the number of slide accidentally, we removed that. But I really want to thank all of my colleagues from the global network who put enormous amount of effort to. Pull this slides together. So thank you again.

Moderator: Thanks Karunakar. For a very comprehensive overview of this liquid based formulations. Thank you. And our next speaker is Dr. Stephen Hoag. He is the professor at the University of Maryland Baltimore School of Pharmacy. He has broad research interest, including several areas like the oral delivery system, controlled release polymers, excipient functionality, 3D printing. So I welcome you to kind of talk to us like he will be talking about the 3D printing. Controlled release dosage form in distributed manufactured networks. Thank you.

Stephen Hoag (Baltimore School of Pharmacy): All right. Thank you for the opportunity to speak this afternoon. So talk about 3D printing as just mentioned. Here's the outline. So talk a little bit of an introduction of 3D printing. It's a relatively new technology, at least in the pharma world. Some use cases for 3D printing. What develops the quality? What are the 3D printing quality attributes and then also the look at process analytical technologies in the monitoring? Of printing and then finally a summary. And throughout the way I'll I'll talk about my the research needs and things like that. Some of the things that I'm gonna say about 3D printing, you know, everything that's said today applies creates a dosage form. A lot of there. A lot of overlap with the existing technologies, but there's also some differences that we can look at here.

On the right side, here is the traditional way of manufacturing. Or something like a tablet and the tableting and capsule making are well known. And they can produce things very rapidly with the 3D printing. It's it's considered additive manufacturing. So it actually goes through a process where either a powder bed is made or something is extruded. And the beauty of 3D printing is that you can get exquisite spatial control. Of where the components are. So that's and also. You can have multiple nozzles and you can have different ingredients intimately mixed together in a spatially precise way, and when you look at like traditional tableting and things, that's really not possible to do to that same level. I could make a tablet within a tablet or a multi layered tablet, but the control over 3D printing is much more. Also, they're kind of the advantage that of customization. So if I had a tablet press and I wanted to switch over to another tooling size or whatever, that's a mechanical change out with the 3D printing, those changes are software based. So if I wanted to produce 100 tablets in the 3D printing, I could. Have all 100 tablets

different tablets made in the same batch? So the software versus mechanical change out, so that's. A in terms of customization, that's probably the big advantage of 3D printing.

Here's some of the use cases. There's one example of a commercial product out there that's Spritam ziprasidone. And as I said, there's one commercial product that I know of some of the use cases are are being considered like rapid production for clinical supplies. And if you look at the right side here, here's something that we've done our lab where you can print this out and you can just literally with a spatula, put the drug in there and weigh it. And produce these things. So if the drug has good solubility, like BCS class, you know that's one and two that are. Know one in the soluble ones. It works well. The insoluble ones you may have to add excipients and things like we're talking about. The amorphous solid dispersions of things, the other things because of the spatial control. Long acting implants devices is A is a. Big area, maybe a little bit beyond what we're talking about today. But that you'll see that and that's particularly important for modified release. Hospital compounding is another possible use to date. Most of the work. Is based on kind of immediate release, but when you look at all these possibilities of controlling polymers, you can see that it won't be long before modified release is will be considered.

There are different types of 3D printing. These are the most common. Some of these involve forming a bed like the binder inkjetting, where you form a powder bed and then you spray things on there. There's fuse deposition modeling. Where materials extruded through a nozzle. Here the semi solid again, a nozzle extrusion direct powder nozzle extrusion. Here's stereolithography. And selective laser centric, the next slide kind of shows some of the differences here, the systems that have a nozzle, the actual filament material, the material that makes up the dosage form is what's extruded with these powder bed systems. The what is extruded? There's a powder bed. It's formed, and then there's some kind of binder that's put in there to hold those particles together. So you can see, you know, we're talking about 3D printing and things you can produce things inside and outside and get exquisite control over that. And with this type of system, you can have control, but it's a little bit more limited. One thing when you switch back. And forth with these types of systems, you do kind of use up a lot of material. So again, if you're doing mass production, you know that. May be an issue.

So these are the the, the basic kind of differences here. And how that can be broken down and then we can look at the the 3D printer here and here is just showing this particular printer has the, you know these three different systems, the direct powder and all that the filament and these different heads they can all. Produce on the same product or you can make different products and to kind of understand. And where the quality comes from, it's useful to think about. You know how this process works? So so. As I said, it's kind of a software based system. So the first step is really conceiving what you want as a dosage form. And there's lots of CAD software out there that you can create that dosage form. Then you need to take that concept and convert it into something you print. And to do that, there's something called Slicer software. So you have the CAD software to create a standardized file. And you know that the printer needs to know what is the outside surface, what is a wall. What is the internal surface? So the CAD software. Kind of sets. All those parameters up and then the slicer software. Creates the object and it creates what's called. Here that tells the printer you're going to move to the left 1mm, and the temperature of your nozzle will be 60°. C Except you know and all these parameters. And so you can put in a lot of different parameters into that. So you get exquisite control over all of those types of things.

I'm gonna try a video. I don't know. All right, so there was a video there. Let me see. Oh, there it goes. There's this guy showing a printing of a tablet so you can see that it first goes around on the outside there. So it creates the wall that is a parameter. That it is put into that Slicer software. It defines how thick the wall is, and then once it does the wall you can see it going back and forth is now putting a layer. Don't worry, this is not a real log video, but. And so it prints a layer and then once that layer is finished, it does the next layer wall. So you'll see it goes back. And then it will do 22 rounds on the outside and then it will print the next layer. Notice that it's going perpendicular to the lower layer, so if you look at the the view there you can see this is kind of the view here where you have these walls and that's, you know you got the CAD program. But how thick do you want the wall? How thick do you want that inlaid? And then you can see you can make this perpendicular. So you could make this as porous or as dense as you want on the inside. And I just show this in comparison to. Traditional tablet where you have these powders, they're compressed together and things like that. So and I could have put a different nozzle on there with different materials. So you get a lot of exquisite control.

So that's kind of introduction to the 3D printing and so you know one of the things we're looking at is how do you ensure the efficacy, in other words, does it have good bioavailability? Does it have good mechanical strength and then also safety? And again, there's a lot of overlap with traditional. Dosage forms, but there are also some differences and so you know, we're looking at how does one control, how does it ensure that the product is produced and does the 3D printing produce toxic materials? Those are of concern and you know, are there differences in how you assess these things? How do you assess the bioavailability? Again, there's a lot of overlap, but there are some differences, and especially if we're looking at the long acting products there, there could be some differences there. And you know, again, what are the best ways to measure that?

So when we look at that, we went through the CAD software all the way through these steps, we can kind of break it down. What are the things that affect the quality? Certainly the material properties and there is some overlap with like hot melt extrusion, so the viscoelastic flow when you heat that up and make it into a semi solid, how does that flow? How does that affect it? Typically this is done above the Tg. So what is the rheology in the rubbery state? Also, with some of the other systems, there's the powder density, so you form that powder. What is the density that can be affected? And then another critical factor, the material is what is a cohesiveness. What is the adhesion and cohesion between layers and things like that? Other things that can affect that are like the geometry and you know the thickness and all that and I'll give an example of that in just a minute. And then the slicer software, do you have a thick wall? Do you have a thin wall? What is the porosity? All of those are software controlled things. We're kinda looking at how that affects the consistency and things, and then with the printing you know the speed that that head has inertia. So obviously you wanna print as fast as you can. That's a downside of 3D printing is. It's a relatively slow process as compared to a tablet press and so you know the nozzle size, the layer thickness. All these things will affect the quality and in terms of research and how do those that porosity, how does that affect that? If there's combinations and the nice thing with a 3D printing, you know you talk about fixed dose combinations of a tablet with maybe a bi layered tablet or something with this 3D printing you could program in you know not necessarily a fixed dose. You could have a variable dose combination. Maybe to accommodate a pediatric patient with a certain, you know hepatic failure or some type of situation like that. And then one of the things we're also looking at is air detection. Obviously, if

you can detect airs, that is very useful and some of the PAT tools that can do that. And there's more need to to research that here.

Just looking at the material properties, this is just kind of showing you this. And a lot of this is very similar to hot melt extrusion, but one of the differences here is just showing you one layer here and another layer here and then this is showing how this black polymer, which is may or may not be the same as the Red Polymer depending on how you have the system set up, it diffuses across that interface and it interdigitates and that really affects that and the in the way that's analogous to latex coating the coalescence of of the coating. And things. So how much this happens? That depends on the Tg. How fast the printer is going, how fast it cools? One of the things that you have to worry about when you're printing is if you heat it up too much. It will flow after the the printer does, so there's a balancing act and things like that. So so. Anyway, this and this is just showing the the diffusion across the interface, this concentration profile. So that's very important mechanical strength and we're doing studies at that, but it's really uncertain how much that affects variations in that will affect the release rate. So.

Here's some of the other things in terms of material safety concerns generally, like with the the hot melt extrusion or the the filament method. We're actually using very similar polymers that are GRAS, but some of the exciting technologies are with the photo activated systems and we've actually done stuff with like the two photon polymerization, and we've almost been able to print particles that could be injected. We're not quite there yet, but you can print literally with this two photon method on the micrometer size and I I think before long we'll be able to even get down to like something on the order of five or six microns. But the key thing here is you have reactive groups and photo initiators. And then you shine light. God knows. And that's another nice thing is light. It moves very quickly and you can control his movement very precisely and with photo initiators. These things polymerize together to form some type of matrix. So so there is with you know. So depending on the types of systems. But with these thermal initiated systems. There is still work being done. On what needs to be done, I will say that like in the dental world, when they do the fillings and metacrolite fillings. And they shine UV light on that. There is an example of a photo initiated system. Whether that extrapolates from the tooth to the dosage form still remains be seen, but it is something that's being looked at.

Others just looking at the quality and things you know, some of these parameters just show you. Here's a slicer software and the nozzle size and all that will affect it. You can see here's a wall with a very fine nozzle size. And so that all those how that texture, how that's put together can really affect that. And I don't think it's very well understood how well that you know how all these things will affect the quality all that so.

Here's just some work we've done with these capsules we showed you here. And so there's a you can see there's three different size wall thicknesses and you literally just with a spatula, you just put the drug in those different walls. And here, let me. Here's a dissolution profile. So here's the in the standard dissolution bath and then at about 30 minutes, a little less than 30 minutes. The 1st wall the thin wall breaks down and then the drug is released and you can see that. As shown by the the color here and then after about 60 minutes we got another half a millimeter of wall thickness. You can see about 30 minutes later. Again, you that second wall breaks down and you get another bolus and. And then finally, here is the final one. And so one of the things the material properties that the variation in that wall thickness, you know you see this here, but when you kind of go up to these SCMs. You can see that there's a more detailed structure created by that, but it's kind of interesting to see that when you look at this. What are the factors

that affect that variability? But you know, for clinical studies, if the drug is highly soluble, this type of system may give you a lot of things that maybe you could use it to study multi phase AUCs or multipart AUCs or something like that, but. So. So anyway.

When looking at generics, you know there's all sorts of questions, like if I had a 3D printed controlled release, could I duplicate that with a layered tablet or a tablet in a tablet or something like that? So. So you know these types of things. There's no generics, but hopefully someday they'll be coming. And so there's not a lot of research on how to establish these differences. What are the key questions? So that's something I think it needs work. And then the point of care. Like compounding pharmacy, what? What is quality? You know you're making a modified release form here. How you know? Like it's one thing with immediate release and you grind up a tablet and compound that. But if you're doing some kind of modification, does this manufacturing of how, how rugged is this? So there's all sorts of questions that need to be. Done with this and I know in Europe I think there's a fair amount of work in hospitals looking at use of 3D printers. You know, with these filaments in some ways the business model is that the company would sell these filaments and then you would just load it into the 3D printer and print something to customize to the patients and then kind of the the final area is.

What that going on to this question of point of care, what some of the? The things that we've done is these now micro NIR spectrometers. They're actually very inexpensive and we can mount them right on to the thing and actually look at the layers. The final tablet as it's being printed. And this is kind of showing how the measurements done, but you can see that you can mount that on there and monitor in real time and we've done some things like we've been able to predict. The the release rate, the dissolution, the assay content uniformity. We were actually doing some work with machine learning models like neural networks and things like that. Traditional PLS and singular vector machine. You know those models and so, so some things you can predict very well this dissolution's a little bit harder to predict. And this slide here just kind of summarizes, you know, the things that I think need to be looked at the the material science, the adhesion cohesion which is much more important than a lot of other things. Product design what are the allowable dimensions? What provides rigidity? Is there a way of testing for generics? Is this you know, if you look at something from 1 dosage form to another, what are the things that can be looked at? And then also how you assess the patients? I think that has a lot of ability if you have the models to, to control quality and things like that. That's my talk. So thank you.

Moderator: OK. So that concludes our first part of this session. Very, very, really thought provoking. I mean very stimulating talks that we heard from y'all and as I said like you know, there is much work that FDA will be taking back hearing all this to like you know look into what we will be doing as part of the research for 2025. So with that, I think we can take a break. Our team coffee break until 3:20 and then we come back for the panel discussion. Thank you all again. Please.

Panel Discussion

Moderator: Hello everyone. Now is the time for the panel discussion for this MR session. So besides the panelists from industry and academia side, we also have FDA panelists and they are Dr. Manar Al-Ghabeish and Manar is a senior pharmacologist in DTP 2. That's Division of Therapeutic Performance Two in Office of Research and Standards in OGD. And we also has an FDA panelist at Yuqing Gong. Yuqing is the senior pharmacologist in DQMM in ORS OGD, and Dr. Likan Liang. And he is a supervisory pharmaceutical scientist in DPQA X in OPQA II in OPQ. And they also have a Dr. Hailing Zhang. Hailing is the division director in DPQA XII OPQA II in OPQ, and we also have a Dr. Zhen Zhang. Zhen is a master pharmacologist in Division of Bioequivalence One in Office of Bioequivalence in OGD, and we also have a Dr. Ahmed Zidan, and he is the senior research pharmacologist in DPQR V OPQR OPQ, CDER. OK.

And so let's start our panel discussion and thank you very much for the really informative and stimulating presentations from our speakers. And basically there are four areas covered related to the MR quality bioequivalence and the bioequivalence global harmonization. So there's four areas. Modified release additional strength waiver and the second is a potential tool in vitro for the in vivo performance prediction for the MR drug products. This is TinyTIM. And the third one, it is a partial AUC and a time based BE metrics. And the last one, it is the novel modified release formulation including 3D printing drug products and lipid based formulations. And so our discussion will focus on these areas and but if there are any some other topics and that is still related to the MR BE and global harmonization that's that is welcome as well.

So let me first open to the audience in the room. Do we have any questions or comments or suggestions on the research gaps to FDA? You know, so this is definitely going to help us to determine the research priorities. OK. Yes, please.

Russell Rackley: Yeah, I don't want to get talking about the specific topics we heard about, but I had some comments on Charlie's presentation. Yeah. Please go ahead. You know, I it was you always find a way to keep us awake and, you know, engaged in into the presentation. Appreciate that. Regarding the partial AUCs, I see them a little bit forcing profile similarity in one context, but in the context and I you know, I agree that those are problematic and in some cases. In the context of onset and offset. For products, I don't know that the agency is totally ignored the time element because. They would have to comment on this. I understand they're typically set on some appreciation of clinically relevant time frames for onset or offset or maintenance of effect now that. The concept of using Tmax is interesting and I think it kind of gets into thinking about how would we use Tmax. To gauge, you know, some similarity of profiles, but that's a totally different discussion. I thought I would just mention that.

So we keep that in mind. Your proposal for some widths are interesting there, but you know talking about the transition of a minimum effective concentration. That assumes there is a relatively steep PK-PD relationship there so you know I get that. And if you could define that very well for any particular product, maybe that your proposal would work well that seems to be like it might be challenging to do in in some cases though. So those are my comments and I invite panel to weigh in. As they feel appropriate.

Moderator: Charlie, do you want to give some response?

Charles DiLiberti: Thanks, Russ. Regarding, I think the only thing I want to comment on is well, maybe Tmax as a PK metric is I think well established to be not a very good PK metric.

Because it's at the top of the PK curve, so it doesn't tell you anything about onset or offset which occur well before or well after. And as you know, if the PK curve is relatively flat as some of these PK curves are a little change in the concentration at the beginning could drive the Tmax way earlier or way later. You know, so anyway, and using minimum effective concentration, as I said may not work because you're gonna have PK profiles that have such low concentrations. They may not even hit the minimum effective concentration. So you need a variable. I think a variable threshold concentration to use to define onset and offset.

Manar Al-Ghabeish: Can I comment also? I just want to mention something about. The way we add partial AUCs in product specific guidance because it's not solely you know to onset, we just come up with that number. There is usually PK-PD relationship that actually the sponsor conducted and This is why we pick up depends on our study. If there was a basic concentration, what was the time. So that was the basis of this. You know, the addition and partial AUCs. Thank you

Moderator: Zhen can I add a comment?

Zhen Zhang: Sure. Yes. So yeah, great. So from your presentation seems that we use partial AUCs similar as the average concentration, but we as Manar and also Russ mentioned so. Actually did not completely. completely ignore the time so because if you look at the unit of partial AUC it has hours in that unit. So the hours is specifically selected, so for that partial AUC and another comment is. So we don't use partial AUC as a standalone parameter. So we combine it with Cmax, Tmax and AUC to make the final determination. And so when you have same Cmax, Tmax and A comparable Cmax, Tmax and AUC and additional partial AUC parameters for comparison. So how likely the whole profile will be very different? Yeah. At least to me. I haven't really see such cases where we have all these parameters similar, but profile drastically different. Yeah, that's my comment. Thanks.

Charles DiLiberti: OK. Just one quick comment on that. As I showed you can have the same partial AUC in very different PK profiles within that partial AUC window. So partial AUC doesn't necessarily control what we're trying to control, right?

Zhen Zhang: Yeah. So in your slides, I'm not sure. Probably I missed it. So for you did not really show AUC partial AUC 7 to 12 hours. So it looks like in that range, so probably a T/R ratio is outside of the range. So you show the zero to three and three to seven, but if there's no comparison for 7:00 to 12:00, which is recommended in the guidance in your. The profile seems they are very different.

Charles DiLiberti: Yeah, I think that's true. I think in that particular example 7 to 12 was different.

Zhen Zhang: Yeah. So if we take the whole picture into consideration, yeah. So in that case, most likely we are not going to consider it equivalent.

Moderator: OK, Lei has a question. Please go ahead.

Likan Liang: Can I comment a little bit? Am I allowed to speak on, you know, from my past experience, instead of the FDA's perspective? OK, so I came from the industry and was involved in the design or the modified release products. So one question we will ask is do I need IR portion for my modified release products? It really depends on indication and mechanism of actions. So for some indication like those psychological conditions, you know like those. You

know those migraine treatments or pain managements and some of those indications, you really need something to act quickly, so you need a portion in there now. I also want to make sure the coverage of my in my product how much duration I would cover. So I need to allow allocate how much IR for that phase and then I want to like I want to cover 8 hours right and then I need to use the rest of the dose to cover that.

So there's a ratio IR and MR. Or uh, I need to fix it so that possibly AUC, can you know, measure that kind of portion, right. And one thing though. You really need to get to some kind of concentration for the patient to feel the effect so-called kick effect. I need a kick effect for that kind of indications. So I think you know possibly AUC have some merit in there. In order to measure that part of the dose so. Yeah. Thanks.

Moderator: All right. Thank you. Let me please go ahead.

Lei Zhang: Thank you, Charlie. I'm kind of follow up on Russ's question because I know in M13B we did recommend even for IR, not this is MR session, but in IR guidance we also put partial AUC or Tmax to ensure the quick onset. So I don't know if you. Would have been sending us some comments, or maybe we can have follow up discussion offline or you want to comment, right? Maybe we can follow up offline. Or you want to comment quickly?

Charles DiLiberti: Well, as I said before, Tmax, I think is not a very good metric for anything.

Lei Zhang: Yeah, I think the reason, yeah, partial AUC is in more like time average less variable than Tmax. But I think that's the reason. Just want to ensure you know the early part was covered for something you need a quick onset, but we can certainly discuss offline.

Charles DiLiberti: OK.

Lei Zhang: Yeah, 'cause the that could be something you can help. The input for the M13C potentially.

Charles DiLiberti: Sure, be happy to.

Lei Zhang: OK, thank you.

Moderator: Please Anna.

Anna Schwendeman: Hi. So I'm Anna Schwendeman, University of Michigan Co-director of Center for Research on Complex Generics. With Jim Polli, I would like to ask a little bit contrarian question and I wonder all of your opinion. It's it's very common for the agency. I mean, it's required for the agency. All this required to set up dissolution, testing the dissolution, testing for oral products. Simple oral products are complicated. Oral products dissolution testing for complex products, complex injectables liposomes. And my major is in physics. I actually finish. I have degree in physics from Caltech of Russia. My friend is on Higgs boson paper the author, so I know when you take a pill and I think Stephen Hawking mentioned that too, you take a pill, it hit the stomach, you know, it moves through intestine. All the physical properties that happen absolutely different than any of your USP2 USP4 any of the USP systems. Similarly, you take the liposome and that's required. That's required the dissolution of the drug of liposome, when literally from liposome, right? But you inject the liposome in the blood and boom, it's attacked by lipoproteins. It's not like there is water in, it's a picture. There are lipoproteins. High density low density is a real protein. That binding is pulls apart. Actually some

pull apart faster than another. Only way it folds up but really fast. Doxil is stronger, more protected.

So the physics is completely different. Like 100% different between what we are measuring in vitro and between the actual physiology and now we're living in the world of AI. You know, we could modulate the drug, we could modulate the system, we could modulate all of those interaction. And yet we require in all those dissolution testing and so Agilent makes a lot of machines and Waters makes a lot of HPLCs and we waste a lot of time and solvent too, right? You know the solvent to run those methods and you know the world is warming up, right? Because it takes some energy to make the HPLC. The vials, the solvents and recycle them. Environment is changing their global warming press propellant, but how about? I see the nitrous oxide that we use everywhere. So I'm just wondering if you guys could make a comment because it's everywhere. It's like inside from, from one regulatory body to another to another to another.

Manar Al-Ghabeish: Sure, I could start. So first of all, we don't only rely on dissolution for anything, right? You know, when we do quality and having colleagues from OPQ and you know in bioequivalence, we don't only rely dissolution. So yes, I agree. You know only dissolution will just give you one perspective, but it's not going to give you a complete perspective. So This is why we rely on other stuff. And you know, at least you know, and I leave the OPQ to comment. You know when when you are doing. This test bioequivalence, right? You do it on the one batch or you know how you gonna later on for quality perspective can check from batch to batch? Are you gonna keep doing bioequivalence on batch to batch or you know if you're checking for the different strength, are you gonna do bioequivalent for? Different strength and that is where you know there's other perspectives to dissolution, kind of compare and play part of for quality control or for additional strength BE determination. Yeah.

Hailing Zhang: I guess I could add a few things to your question. I absolutely agree with your comment or. Most QC dissolution test method have nothing to do with the in vivo environment. This is because we're looking for QC test to be used as a routine test, which requires certain robustness. Precision. Easy to do. And so that's the reason why over the years we try to encourage the sponsors or applicants at the early development stage to develop some IVIVC. So you could use that simple QC dissolution test to you know to predict in vivo performance. That's the ideal situation, I think. We also see. The evidence from Dr. Shen's presentation were when you have a dissolution test which correlated at a level one to the performance, you actually can use that simple dissolution test which is nothing to do with. It's not a biorelevant but it's biopredictive and you can use that dissolution for managing a post approval changes in the life of cycle management concept. And in some cases you even can use to as a starting point. To develop your generic version.

So I know you mention liposomes. You know liposome, we still require we call release testing. It's not truly a release. It's still a QC test to ensure that from batch to batch you have the consistent quality. That that's the main purpose and we also understand and we in the agency we understand the limitations. Of those type of non-biorelevant dissolution or IVR test? We try asking sponsors to develop these dissolution test has discriminating power against certain recall, CQAs, quality critical bioavailability attributes, but we also acknowledge some of the properties. Maybe it's better controlled by other QC tests.

Moderator: All right. Thank you very much.

Anna Schwendeman: Can I just ask? So, actually excellent news. Excellent, excellent answers. I I do understand. I have a follow up question small one. So I run the Center for Complex Generics right? So and what I hear from my constituents, the industry that many times you put the tablet in the dissolution system and the drug is so insoluble. Well, it just fall down and it's right there. It's right there on the bottom of the of the system. And you have to add a lot of stuff up then to just keep it up and floating. And then I myself developed dissolution test for liposome and I know it has nothing to do with it's you put it in dialysis bag. It is a membrane, so all I'm measuring is through my abilities through dialysis membrane or there is long acting injectable in Vivitrol sustain and Vivitrol triesna. This is designed to go over. Six, six months, three months, one month and we increase the temperature. To be by physiological temperature to facilitate some dissolution just for PLGA or for crystals, it has to just put a lot of surfactants again.

So it's kind of like. So that's perhaps this is the. And then we also require plus minus 5% on those tests. That's what I understand from the review, even though only HPLC can provide plus minus 5% and there is no science around the statistics this. Shouldn't be plus -20 percent, 15 percent, 10%. And maybe you don't have to answer, but this is what I would like to for you all to think about and as a center. Hopefully we could do a workshop and then we could all actually debate the scientific question because at the end of the day this is a scientific question and we are here to improve our science and conduct of science.

Hailing Zhang: Yeah, yeah, yeah. We really appreciate that comment. You know in the FDA we acknowledge. And limitations of the current kind of practice. That's why I keep repeating this. We encourage the applicants develop or sometime. At the early stage. So so to make sure your your testing actually has some type of a biopredictive capability and that's how we can best utilize those in vitro dissolution test or IVR tests. Thank you.

Anna Schwendeman Thank you. Thank you. Thank you for your answers

Moderator: Thank you. Sammy.

Sammy (?): Fantastic presentations. I have a couple of questions to Lieke and one question to Charles. So I'll ask all my questions at once. So at the beginning you said that we need to move away from animal. We need to move, but we are moving away from animal models. So my question to my first question to you is that? How what can we do or what do you propose to make something like TinyTIM or TIM universally available, especially in parts of the globe where they have limited resources? So that's my first question. My second question too is and I give credit to Nella Farfour for that question, which is. What needs to be done or what is missing? Or how can reach the point where we can use? TIM data into regulatory submission. So that's these are my questions to you and my question to Charles. Charles, I'm going to make a statement and I want you to tell me what is the flaw in my statement. So my statement is that when you do, when you do partial AUC. We defined a time and we're asking what is the average exposure during that time frame or you call it the average concentration. But the argument that you're making is that you're saying we need to define the concentration first and then determine what is the time to reach that concentration. So to me it seems to me both arguments we are talking about the same thing is just that semantics are slightly different. So I want to hear from you. So these are my question. Thank you. I'll go back.

Moderator: Yeah, Lieke. Please go ahead.

Lieke van den Elsen: Yeah. Thank you very much for your questions. Yeah. Your first question regarding the resources and how we can make the, yeah, the models more available maybe worldwide. Yeah, that is quite a complex question I think. Well, we of course provide our services to everyone, but I do acknowledge that maybe in certain parts of the world, yeah, this is sort of an expensive service that we offer for the moment. So yeah, this is definitely feedback that I will take back home and discuss internally how we can maybe facilitate this in a in a better way. And then with regard to the regulatory submissions, yeah, I think this is also a good question. I know that many of our customers do already use the TinyTIM data in their regulatory submissions, but of course we are not involved in these submissions ourselves. So it's not for us, a very transparent field. Unfortunately, we tried to discuss this and get further insights into this, but for competitive reasons we do not always get a complete understanding of how the data is being used. So I guess you probably have a better understanding as the FDA how the data is currently being used and what you would maybe like to see differently there. I guess we are both working with the same industry partners, so I think it would actually be really a big gain if we. More closely together on what would be needed to get these applications in a better shape. Yeah, for these approvals and I guess also that comes back maybe a little bit to my last slide in the presentation and that's for us. It's not completely clear what's the guidelines are and what the guidance would be. So it's also very difficult to communicate that to the industry that we are working with. So yeah, clear guidance on this would be really valuable I think for all the parties. Involved and yeah, I would really love to work more closely together on getting some of these. Yeah, in a good shape to communicate. And that would be really great, I think. And I think that can really accelerate the field and the generic field as well. Thank you.

Charles DiLiberti: By the way, doesn't your company offer dissolution with your TinyTIM as a service for those companies that can't afford to buy a TinyTIM system?

Lieke van den Elsen: Yeah. In fact, we do not sell the equipment at all. We only sell the service, but I guess maybe, yeah. What they were referring to is that the service can of course be

Moderator: I think I think this conversation can be outside. Conversation. Yeah.

Moderator: Charlie, do you want to very shortly response.

Charles DiLiberti: So the human body responds to certain levels of the drug, and if you're below those levels, you get little or no response and it makes a difference. The shape of the PK profile within the time window when you're calculating partial AUC and you can get the same partial AUC as I showed. With very different profile shapes, some of which will create a clinical effect and others which will not. So it does make a difference. Using partial AUC is insensitive. Towards some aspects of time to onset of action, whereas the metric that I'm proposing should be sensitive to those at all times.

Moderator: Thank you very much. Really nice discussion. So let's move on to the next topic. Additional strength waiver for modified release drug products. So in Dr. Polli's presentation, he indicated that there are still challenges in the drug release and even product innovations. The proportional similarity across the different strengths is for the matrix drug product, right? And also conducted a survey and to get this opinion. Suggestions from industry and at the same time, Dr. Jie Shen also presented her research results about the strength scaling for the ER,

drug product, and she indicated that there are some kind of a safe space for the release controlling critical excipients even without the formulation proportionality. So you know. The question to you too is what are the factors? Do you consider they're really, really important? To the additional strength waiver for the modified release drug product and what kind of research, do you think we should conduct to fill this gap?

James Polli: Umm.The one that was the fact that was sort of graded the most harshly was similar dissolution across strengths. So I, I, I and I agree with that it so that should be probably more important than composition, especially if you have a good understanding of all what's going on with the composition. I'll just say one thing about the results I didn't mention is the second thing. That was sort of most harshly. Was similar dissolution between test and reference, and that surprised me. I know it's nice. But it just seems like it's a nice thing and that I understand last, especially if there are differences between test and reference. I don't know why you would expect the dissolutions similar to be so important. So that aspect. That element I think is worth researching in the context of product understanding of the test, yeah.

Jie Shen: Just to add on that. So in addition to product understanding, we also talked about. Even in this morning's session, how can we identify biopredictive, in vitro dissolution testing methods for some time when we test the products across the strengths or test product reference product under different conditions, we might have different results. So I think we need to identify. More predictive, in vitro dissolution testing. TIM methods or suitable methods for different types of. MR drug products, I think in order to do that, we need to utilize PBPK modeling because that can help us define the not just the specification, but also help us evaluate and compile different dissolution testing methods and conditions and technologies to have a more predictive dissolution testing method. Available.

James Polli: I guess one thing I would just add about sort of product understanding, seems like everything comes back to that is I do think we don't do enough in vivo testing. In terms of understanding products, at least in the public space, I know companies spend a lot of time and that sort of thing doing that. Although they also say that they don't have time to figure everything out too. So it kind of makes me wonder sometimes, but I think research that has an in vivo component. So we can say we understand what's going on would be very helpful. I mean an infinite number of times we've heard we don't really understand what's going on, even though some of these formulations are been around for quite a while.

Moderator: Any additional comments from our FDA side?

Hailing Zhang: Yeah, I I absolutely agree with Jim and the and the Jie's comments. You know, I think if all the research teams point out, you know, MR forms, it's challenging for a waiver for additional strength, right. That's why our CFR actually exclude that. And the product understanding is important, but I think this is circle back. My original comment like if you could have a dissolution test. Which has the correlation with the in vivo performance. Then that dissolution test may have lots more value and utility when you try to you know, although we exclude MR additional strengths by waiver in CFR, but we do have a scientific bridging approach at least for the so. Where you know? Obligation. Actually look at the NDAs space. If there is a scientific bridge approach proposed for additional strands and from scientific bridging perspective, I think both you know IVIVC and the PBPK we saw they have been used to kind of

utilize to waive additional in vivo PK studies. I think there is a certain, certainly there is a space there. You know, so. So I absolutely agree with Jim and Jie's comments. Thank you.

Robert Lionberger: So I would just like to ask our panelists again. I think you know Jim framed it. I think at the beginning, right. Showing that the recommendations from the EU make your formulations proportional right, and I would say, do you agree with me that that seems to be contrary to, as Anna said, physics, right, that we ought to think about the mechanism of these formulations and design them that way. But you know, so you don't. You don't have to say you disagree with all of Europe, but that's that. That's, but I think that there is this long standing even. Within FDA, a lot of people are really attached to proportional formulations are the most conservative, cautious, safest thing to do. And you know, and if you know and if you still think that that's uncertain, I think you want the feedback on what type of studies and research would. Help really provide the foundation for that question because I think that's the core of what we're trying to do on the modified release strength waivers is. Come up with what are the best practices for designing consistent formulations from a mechanistic point of view, given that you know the dissolution methods may or may not be. You know biorelevant and you know if you had a great dissolution method that you knew was biopredictive, you would probably just follow that you know and here you're in a state of more uncertainty. Maybe your dissolution method is not as sort of predictive, but if they're similar and they follow the right physics, that's the risk management that you're proposing. So I encourage people that you know more a little bit more comment on that because I think that's the important thing about the direction that we're thinking about the research and activity here is what can help. You know, fill out that case there and say what's the best way to do to design products that have consistent behavior across the strength? So welcome the direct comments from our panelists on that question.

James Polli: Since I'm not, yeah, I think the work that Jie's doing is quite good. I mean, I do. My impression is HPMC based matrices are sort of #1. But don't stop there. You know, I'm not sure what's #2. You know, probably some, I think coating systems are probably even more risky actually. So in some ways that. Even if not as common, certainly that would be a priority. I would think too. So if somehow there's a way to identify technologies in terms of their overall importance? And then maybe weighing risk, do the sorts of things that she's doing in terms of. You know in terms of formulation understanding, at least the in vitro stuff, yeah.

Manar Al-Ghabeish: I just want to have a comments about the survey, like I'm kind of happy that generics actually thinking about dissolution to be a factor like that's like #1 which is I totally agree. But the second factor was totally surprise too, which is go back to Anna's point that when a generic come with a dissolution, it's very specific for their products. So which is may not apply to the RLD the same way. So you're not expecting it to have. Same, you know the dissolution all over the different strength of RLD base. I'm surprised that generics is thinking that way.

James Polli: I guess my two cents would be. I think that's a natural target though. Which probably points out again the product understanding part and I think it does relate to Anna's point about dissolution. And I mean, I think in terms of compendial dissolution versus non-compendial dissolution. I know a lot of people want to do more non-compendial dissolution, but they're often. It's often not advocated, right? It's easier to do compendial dissolution and the joke in my lab is you get to go to lunch earlier too.

Ahmed Zidan: I think I can just consolidate all of our comments into just like a couple of phenomena that we need to pay attention to. First of all, all the understanding and the lesson learning during development of M13A for immediate release cannot be straight for the extrapolated to modified release. So. So the interactions that's happening of the drug substance with the physiologic condition inside the body. This is totally, I would say, controlled by the dosage, form design and even the research that we are doing with the matrix system, not necessarily. To other dosage form design, I'll just give you one example. Like most of the researches that we are doing with with matrix based proportional formulations, we can control it by just limiting area. The surface area for for diffusion. In this case the decrease in the surface area. May not be affecting this proportionality, and in this case we can have some sort of, I would say more control over the bioaccessibility by the formulation design itself rather than physiologic fluid and the presentation of API to the absorption window will be played completely by the dosage form design, so I would say. The first step to do is understand your formulation design. And dosage form a design very accurately, the interaction with physiologic fluid started with a sensitivity analysis. I appreciate all the efforts that TinyTIM like they have done with the TinyTIM, all the complication and TinyTIM in considering most of the physiologic like conditions there. But but do really need all of. These complication in all the cases to come to a conclusion I can say no. Right. It depends on the design of your dosage form so in some cases the gastric emptying rate is a critical factor for availability or exposure of the drug to certain absorption window. However, I can mask it by the formulation design, right? In this case I can also remove the gastric emptying rate from my risk factors. So I would say the first step, understand your formulation. Second step have a sensitivity analysis. Of your physiological condition. What I want to consider among these physiologic condition affecting the bioaccessibility of the drug from this particular dosage form the extrapolation to all dosage form designs to proportionality may not be straightforward for modified release and of course research is still needed to make like more broad picture about.

Moderator: All right. Yes, I really appreciate opinions and suggestions. Comments from both sides. So let's move on to the last question, OK.

Hailing Zhang: Sorry, could I have one comment in terms of the USP compendial dissolution method? Actually we tried to share this message as as much as possible. Actually, we keep telling the sponsors USP method and even the FDA dissolution database. Are the starting point of developing your own dissolution method. The dissolution method should be product specific. We do need this cheerless passage as much as we could because we see lots of questions from industry. If they think a USP compendial dissolution method, they think they're done, they're not.

Moderator: All right. OK. So last the last question, let's move on to the last question. All right. The lipid based formulation is involved in the lipid digestion and also lymphatic absorption. So during the presentation, even you know even from yesterday or this morning actually and there are some kind of lipids assay could potentially help. This is in vivo prediction, but how about the lymphatic absorption? Do you think there's any tool for this prediction? And So what are the challenges to this part? Can start from Karunakar.

Karunakar Sukuru: Yeah. Thank you for that question. And once again, thanks for the opportunity. So with. Lipolysis models. You could certainly rank order the formulation at best. At this point. Other than this SMEDDS formulation where a lot of them have established IVIVC correlation for SMEDDS, but rest of the lipid formulation especially. For lymphatic delivery, the

one available model out there that is is chylomicron artificial chylo chylomicron based system using intralipid or lipid emulsion where the drug would be you know taken by these chylomicrons and. The entire lymphatic delivery is based on the chylomicron taking the drug and delivering it the system, so. But again, it's just an artificial model. There are still barriers to that. It's not like proven, but that is the best that is out there at this point. Yeah, yeah.

Moderator: So hopefully you know later on we could see more available tools to this side because you know potentially that could improve the IVIVC prediction because right that is going to cover the two sides. Yeah. OK. All right. OK. Yes. All right, we already actually run over about 6 minutes. And so I'm going to close this session. Thank you very much for the presentations from the industry and from academia side and also the panelists on both side from you and from FDA. Really appreciate all the suggestions and comments and additionally if you have additional comment and further thinking. Please submit your information through the docket place. Yeah, that's until July 7. Thank you.

Closing Session

Sam Rainey: We are going to transition now into our final speaker of the workshop and then closing remarks. So please join me in welcoming Professor Anna Schwendeman, the Co-director of the Center for Research on Complex Generics, as she provides her insights. Those assembled really by the CRCG based upon input from. Across the generic drug industry. Professor Schwendeman.

Anna Schwendeman (CRCG): Thank you. OK. So go up and down. Uh, huh. And the mouse at the point the laser pointer is. Oh, wonderful. Thank you. Wonderful full service I get from our Sameer here. So first of all, I really would like to thank the organizers too for inviting me and putting me as a closer of this whole. Video for public forum. It's really had been a pleasure for James and us. And James and visiting myself to run the center. I believe we have done a lot of good. And here I will both. Kind of give you a little bit background on the center and then also very recently is the FDA OGD ask us to survey a few more companies about the most current challenges and it's very important to do it periodically because the environment changes. For example, when I started the center, there was no nitrosamine concern and then it becomes the number one concern. Nitrosamine. Nitrosamine, nitrosamine and then CMC and everything else. So. So it's all these changes, the demands and the pressures on generic industries always changes.

So with that, let me proceed. We start establish the Center for Research on Complex Generics in 2020, and this is a collaboration between University of Michigan and University of Maryland and our mission is pretty simple. To increase access to safe and effective generic drugs through enhanced infrastructure, communication, education and research collaboration across. Industry, academia and FDA. So the dedicated to advancing those programs that stimulate scientific dialogue disseminates current insights and generate new knowledge about complex generics in support of FDA mission to promote and protect public health. And I think it's very important to understand today that 90% of the drugs that this country takes. Their generic medication, and yet only about 14% of the money this this. Is spent to produce those generic drugs, so there is a certain strange economics going on. Generic industry is actually having smaller and smaller

profit margin. More and more pressure on amount of science they need to produce in clinical study requirements. Nitrosamines there are higher cost of shipping, higher cost of hiring scientists. The pressure on the industry is quite high. And that much is very clear for us. And yet the money that is made, the savings go to support development of brand new CAR T cells, therapies that cost $1 million, one patient or half $1,000,000 one patient. And this is wonderful. So generic industry in some way fuels the innovation in this country. And then in the other way. We all are the users, so there is some should be some fundamental debate. Outside of this scientific forum, but we are way overdue to the fundamental debate around this particular issue and perhaps we could figure out how to do it.

Alright, so here my primary goals of CRCG. There are three of them. The first one is infrastructure. Then there is education and then there are collaborative research. So let me describe the infrastructure and communication goal because I feel like this is a goal we enhance quite a bit. We we've been quite good in establishing that. So when? Originally, the Center for Research on Complex Generics was proposed. It was clear in the mind of this OGD management that we are missing the big communication link generic company pay into the GDUFA. They pay the user fees and then OGD sponsors research. OGD sponsors research. Outside sponsors, internal research, OGD and then also the whole agency hire more inspectors. Inspections are faster, so you could meet review goals. So it's very important. Financially, very important system, and yet every quarter they have industry meetings and people come generic industry come but because in the room seats, all of the competitors, the chair was the Apotex Sun Pharma, you know everybody at the same table. They're very reluctant in sharing their opinion even around science, because as you share, you also disclose. What products you are developing and it's extremely competitive build as you know in the profit margin is seen and they very much want to be the first generic approved and the products are complicated and there are a lot of issues. So the idea behind creating of the center is to bring in somebody who could translate what is lost in translation. And it took us a long time to develop the to to earn the trust of generic industry. Actually, yeah. So I I feel like there's so many friends of mine here over two week to to two last days to earn the trust of the FDA. And different players within the FDA to. The trust of the outside consultant and companies that benefit from the research and to really understand what is the research needs are I always feel that I'm like in the movie Lost in Translation. I'm here sitting in the middle and I'm a translator or another wonderful movie and a book called Rashomon. The movie by Kurosawa and then the book by Akutagawa. It's very sad that in this country. The art indication is a little bit behind so very few people probably could even understand what I'm talking about, but please read this wonderful book and wonderful movie Rashomon.

So what it talks about that the same event happened, but the three parties see it completely differently. I I remember crystal clear being here a year ago and I was sitting there on the panel and we were discussing immunogenicity of peptide because there is no more important. Aspect that immunogenicity of peptides with GLP-1 making billions and then being the gold rush that everybody are rushing in. It's like, let me grab the piece of California. So here we are. I'm sitting. I'm speaking or sitting here on the industry side and on the panel we have Eric Pang. He's part of OGD representing immunogenicity. We have. What's my friend Andrew? Graves. He is part of Teva representing industry. And then we have another person from company, Ginkgo or something like that, which propose a brand new research. It was fascinating. Because there is a, you know the the statement from the Andrew Graves is like we need specific assays. There are false positives. There are false negative. We don't need some of those testing. You put too

much constraints on the on the test. And then the statement from the FDA, yes, we we do not know. Is it important? Is it not important we trying to protect the public, et cetera, which are all good points? And then the question from the MIT Guy, Ginkgo, oh, I have the 3D system, 3D lymph node, where I could figure out how to solve it. My goodness, what a fascinating moment for me. I still remember it. And Andrew Graves, we don't need 3D. So we just need to know how many dilutions and how many and don't ask us to validate this plus minus 5% is not working at 5% so that was a very interesting. I still come back and remember this this feeling but do understand while I'm leaving my. Own Rashomon the OGD is also leaving their own Rashomon right the front that you see is. Office of Generic Drugs. You see Rob Lionberger. Or somebody from this department. But he has to interface with the Office of Pharmaceutical Quality. He has to interface with the Office of Review. He has to interface with the office of Bioequivalence. All of those offices. And you know, and I'm sure that OGD is trying to develop the better science. Truly I I am after running the Center for almost five years. I guarantee that the intent is the same. You wanna make sure that there you do less of unnecessary research and necessary clinical trials that you have on the table test, in vitro tests to approve the drugs. We all have the same intent. Truly the agency. The industry and all of us who are in academia, the intent is clear because it's important. What we're doing is actually critically important 90% of drugs. Truly everyone in this room take took some generic medication in the past week. Probably. You know, whether it's just an aspirin or whether it's statin like me.

So this that let's go to the next one and then there is the education and training and this mission is also actually very simple, but it took us several years to get to a good system. When we run our workshops that allow now not only me lost. In translation, but everybody come in and sit at the same table. And this is actually remarkable. There was a workshop on complex injectable products that I couldn't attend for some issues with timing, but my husband, who is expert in long acting injectables, he was there and it was the first time he ever attended this workshop. And he said, Anna, you know, if that is the only thing you have done, you should be so proud because here it is. I sit on the table and at the table see the FDA. Sits generic company and sit. Some. Me. Yeah. Myself. Academia, where USP and other agency where else would you have a conversation like that? An open conversation can the conversation of where is the scientific problem is trying to answer the question that I ask just, you know, in half an hour ago. And then the collaborative research and at the moment, we did just a few small projects, but hopefully if the center is renewed, we would like to start answering big questions. Sameer already come and says stop talking. Yes, OK.

So is that a big questions like how do you approve Invega Sustenna and can you develop in vivo and vitro correlation, right? I mean, you don't we? We need more and more psychotic medications. Unfortunately, after COVID more and more people requiring some sort of medication, and yet they're wonderful drugs. But to run the study, it takes six months, right? Six months. Three months. One injection. This how long it act. So how do you do it? How could you really prove it and what it is physically? It's a particle size hydrophobicity, the dissolution. You could probably use a mass model to predict this whole, but in order to prove it in a person we have to have industry participation. We need somebody who would make PLGA particles of different sizes. Right. You know, a broader distribution on their distribution. Or a mixture of large and small. How interesting. And also the big projects, a big undertaking and I hope we're gonna do it for next year, OK.

So with that, I'm sorry, those are all my friends right here. You see, those are the friends we talked to, the one who by now trust us. The one who, you know, we could take selfies with and laugh about. Something and tell me the most interesting details about the effort in developing of the drugs. So this is. All the companies we interview over the years and then the recent ask the three topics come up. So the first one is complex API characterization and immunogenicity. Including peptides again and including nucleotides now. The topic in the middle? You could talk forever. I could speak here for the whole 8 hours just about this topic. Complex product including long acting injectables like Invega Sustenna and Invega Trinza. Inhalation products. My God, this is the science in itself. Inhalation complex injectables. Again, drug device combination or drug device combination is a big one. Right, there is no. Never more interesting in drug device combination. And now there are also known complex dosage form M13A and one of the reason is the physics. And also because now more and more hydrophobic drugs are about to become generics really. So we used to work with aspirin. We used to work with water soluble drugs and on the cyclosporine and was a big problem with tacrolimus. But now? All of those anti cancer drugs. All of those kinase inhibitors, they're all hydrophobic and they all come in soon. So and variety patient to patient is 50% even if you take this particular drug. So it's a really upcoming issue even for simple products. It's upcoming issue and IVIVC and control release even more of an issue and actually last year I for the first time I've showed it Lieke pointed out. I remember you on the panel a year ago so but clearly. It's a big topic. Today this is so many good presentations. I really if some want me to close, I feel like I almost said enough. But if you want, I could speak a little bit longer and. I I think I said everything but complex APIs and immunogenicity everything we found in vitro assays. How so?

Here this one about oligonucleotide in vitro assays. How to characterize innate and adaptive responses? And we already live through it and in the peptide. And now we are restarting again. Season 2, the same movie. Season 2 is how do you validate immunogenicity for oligonucleotides impurities. This is actually mathematics problem. If you look at oligonucleotide and understand that there is a chiral difference and there are potential for you know it being slightly different and you do the math, truly just do the math. Amount of impurities 10 to the 4th I I do not know. Depends how long oligonucleotide is, right? So mathematically amount of impurities is outrageous. And yet we have a guidance characterize everything to this degree. Measure. How to do it? It's a it's very, you know, just a basic question and then alternative approaches. I mean, can you actually do something that we don't have to do all of it? I don't need to belittle the peptide question. It's, you know, we're moving from synthetic to from synthetic to recombinant. We're worrying about host cell protein. And now there are pegylated peptides going to come. And how to characterize it? So there is all sorts of guidelines around chemical characterization and the you know, how good are the columns. Can they really separate everything? And and this is our gold rush question. So everybody coming here, a gold rush and now people understand, you could have a gold rush. So there are new peptides coming in development while the viral P1 Now there are other millacordin or other peptides that make you actually eat or other type of. So now the whole industry innovators, they're starting to focus on peptides again. So it the project will continue and you need. A regulatory framework. There is need for harmonization. There are all sorts of diversion, regulatory standard and this is, I think has to do with your internal Rashomon because people can't be submits applications this time. Review comes like that and then we submit different peptide. Oh my goodness, they require 10 times more tests and I hear that about, you know, extractable reviews and other reviews. So the kind of the lack of harmonization within how reviews are given. It's a real

problem for generic industry and I think it's it's some institutional problem for you as a your own internal Rashomon.

OK, here you know exactly. I could talk for. I really could talk for the whole 8 hours. Bioequivalence, that's what I describe in the Sustenna and complex. How do you not have to do the clinical study for the ones that last six months? You have to do this clinical study 10 years. This is kind of funny, right? So how do we address that and what are the standards? What the physico-chemical methods? Drug the inhalation products. Oh my God. I always call it pharmaceutical sciences. In one in itself. Here we are. We have a we have a drug, we have a propellant. We're trying to switch from one type of propellant to another propellant. We mix the in the vial here physically. There is a lot of gas and there is a drug and sometimes a little bit of surfactant and you come up with different particle size. You open up this one slightly like that and not only particle size distribution. But also overall hydrophobicity and very surfactant. And if you buy surfactant from a different place, what's going to happen? And this whole thing in the device, my goodness. And then the kid or adult, they have to puff and everyone puff differently. Today you could puff three times every time. Different puff, right? And then it's it's deposit. Different place, of course, right? And then you have all sorts of people. You have a babies and then you have a. All the. All the patients and overweight patients. So you have this poppy K issue. I find the samosa interesting. I didn't know anything about it before I started the center and then I was so stuck. It was just so fascinating.

Alright, drug device combination. I still stay with the same joke as I did last year. Go. If the pens, the one you write with would be regulated using your drug device combination, you would still be writing these big pens. Big. Because clearly you do not understand that sometimes you have to remove the some, some you have to click two times to click somewhere else and of course you know I don't want to belittle, it's important issue. My son has type one diabetes, his friends have all sorts of other diseases, number of autoimmune diseases are growing and we have many different users. All the users, newer users, but we have to come to some middle ground because same comment as I made before. It's environment. It's a gas environment. Is amount of people who do in the work HPLC solvents and also you know those disposable syringes. You know how much plastic it generate. Oh my goodness. Yeah. Global warming.

OK. Alright, now we come into the new one M13A. Uh oh. What is that? I cannot miss that. This is the most important they identified. I think I said it already. The drugs are more and more hydrophobic, so the drugs that the companies working on right now are truly hydrophobic and and this physically hydrophobic drugs exaggerate this issue in the dissolution media. You have to put more and more. Precipitate in your USP for USP to there is all sorts of issues and then long acting injectable and Concerta. My God, I teach a lecture on Concerta. That's the most sophisticated pill out there, and it's using children a lot, right? So how do you deal with that? The pill is just a master work of the pharmaceutical sciences, right? OK.

Many many topics here I released a few and there are many others and I think through the workshops there were so many proposals. I really do not need to go over this in more. Details and in summary, we've been in function almost five years. We worked very hard through pandemic to establish these relationships with everybody. Actually with generic industry, with various players within FDA, this outside thought leaders with academic leaders, we have this wonderful. Ability to come closer to translate and solve. Find out where the truth. Is where is the scientific question is and with that we also. I will also like to highlight another big need is in education, education and training of our workforce. There are so few students that we graduate

that have enough knowledge to use physical chemistry to make remarks that I'm I said earlier today. There is kind of a lack of basic training in physics, chemistry, physical chemistry, BI. Well, art as well. But then and then the ability to apply it for to farm site, lack of knowledge in H&H equation or solubility or K speech, this is some simple math truly differential equations. So we have to train the workforce that the universities generate, but equally we need to train the reviewer. Somebody writes this has to be plus minus 5%. But no way it could be plus minus 5%. Maybe a + -. 50% is sufficient, and I know I develop biologic product before. So for when I when I was working in industry and I was submitting INDs for biologic drug, our bioassay was plus - 50%. So there are precedents. Clearly, many presidents of actually using scientific judgment to require something.

All right. So with that, I hope you could continue all of it, because I feel like the important link in this whole infrastructure here is some workshops we're still planning for this year, hopefully on particle sizing, something tremendous. Listen, Billy, it's very important. You tried. Many people measure particle size. You come up with completely different answer. You use different method. You use different person, different day. It's fascinating. Some some people Potter dust drop in your crib it. Oh my God. And yet the same thing is review analysis plus minus 5%. There is another one using artificial intelligence in genetic drugs. I'm very excited about that. My own son is working for a Unicorn AI company Sakana AI in Japan, spending the whole summer for months. You could look it up. AI scientists, they come in for our jobs. They gonna do everything. So it's very interesting, but there are clearly very smart people using very good tools and powerful GPUs to solve the problems. I have a lot of. Hope for that, I truly do. And it's wonderful that you are embracing it. And then we have another one around generic atomic products, another complex in complex product type of work. With that, here we are. We're here. We have a website, we have social media, we have YouTube channel wonderful. On our website you could download all the research outcomes. It took us a long time to put them all there. And we need to acknowledge the funding from the Agency, the Rob and Sam Raney and also many of you who own our Oversight Committee Chairman Andrew Vaillé. There are also Markham, all this very highly involved. And then. We also need to acknowledge our Members. It's Jim Polli Co-director Dan Hamel, and Jen Hock. Thank you so very much. All right.

Robert Lionberger: Thank you, Anna. And the CRCG. So again, it's my pleasure to close out this this event. Really thank all of the FDA staff that participated and especially all of the outside people who came here and participated in our panel and helped us develop, you know, helped us develop this workshop, have the discussions. Really appreciate all of that. You know, there's a lot of people that were involved in working through the logistics on this. You saw them? Some of them at when you signed in and registered. They also helped with all of the organizing. Of the of the session preparations that went in behind the scenes to make this happen. As well as the communications and clearance and of all the materials and coordination of all the planning sessions. Again, the FDA staff at our Conference Center who helped with all of the logistics and having this room and the streaming and all of those activities coming from there. So there's a whole bunch of people that make this happen. So really wanna thank all of them. For their work on this activity, as we as we conclude you know and so I appreciate all of that.

I would say you know, when I look back at this work, so you know the things that I really was struck with is, you know, in our first session how important it is to really move forward with the ability to have recombinant synthesis methods available to the generic industry for competition in the GLP-1 space. Like I think that has to be a very high priority of make sure whatever the

scientific barriers are to the, you know, or psychological or regulatory barriers there to really be committed to moving that forward. And you know, allowing the marketplace to determine what's the most efficient way. To supply these peptides and not sort of our regulatory baggage from the past and really you know really work on the science. So that's a high priority. You saw the emerging area for the oligonucleotide therapeutics. Really, paving the way for generic competition in every modality, you know. Later on the first day thing I took away were the importance. Again, we hear this again and again. The importance in the inhalation products is a complex area, but we have to move forward with simple, straightforward approaches to demonstrating bioequivalence for those products. There's, you know, huge. You know there's very few products in the area that have generic competition. They're essential for the treatments of asthma and COPD across huge groups of our fellow Americans. We really have to be absolutely committed to having the most efficient and straightforward way to do that. You know at FDA. We're committed to meeting with any applicant who's developing those products, giving you, you know, direct feedback on your development programs as many times as necessary to really encourage investment and development of these products. And I think what we heard from here is, you know, the constantly of making. The methods you know, again, a lot of the things that we're asking to do to avoid the clinical studies are sometimes novel. Methods and challenging to implement, so really to work with you on that really work through the CRCG as the community in developing the best practices for those. But you know, I think it's really this, this meeting really showed us again the continuing importance of working through all of the issues in developing and implementing the pathway forward and the inhalation space, you know, and today you heard about. The immediate release and modified release products there and I think the sort of interesting point there. Really is looking at you know, what's the role especially for the low solubility drugs, the modified release methods. Are there? Sort of biopredictive dissolution methods that can really be established and people can have confidence in them. I think this is really not just for submitting them to FDA, but it's really for using a using them efficiently in product development. So you know, even again, if you're doing bioequivalence studies, you you don't want to fail the bioequivalence study. You want to. You know you want to move ahead with these methods and use them. I think this is an opportunity for the CRCG to, you know, to help facilitate. The you know the testing and the development and the proof that these methods work across wide ranges of products in sort of collective Community Action. You know there's lots of approved products where we know, you know, you could go through them and say, well, do these methods predict? The differences that we saw in those studies that the products that are the same, really having the Community establish. How confident these are and what the best practices are for using them for the different types of more complicated modified release, dosage forms of low solubility drugs. The lipid based formulations, the solid dispersions, all of those areas. You know, I think there's, you know, I would say it's not clear to me what the best predictive method is for those products. And I think that's sort of a frontier of the sort of pharmaceutical science that will really be helpful to the generic industry as it did. As they develop products and so with that, I'd like to thank everyone for participating in this workshop and we look forward to engaging with you in future years. And we also look forward to really going back and digesting these comments and really help focus our research activities for. The next year on these most important. Critical issues that are emerging. So thank you all very much. We'll chat again on Friday.