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Session 4: Implementation of the M13A Guidance: Lessons Learned and Advances for Immediate Release Products

Co-Moderators:
Dongmei Lu, PhD Associate Director, DTPII, ORS, OGD, CDER, FDA
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- **Amorphous Solid Dispersion (ASD) Products and Potential Alternative BE Approaches**
  Girish Nihalani, MS Associate Director, Product Development at Hikma Pharmaceuticals USA Inc.

- **Dissolution of Amorphous Solid Dispersions and Absorption of Poorly Soluble Drugs**
  Geoff G. Z. Zhang, PhD, FAAPS Founder, Chief Technical Director, ProPhysPharm LLC

- **Modeling & Simulation Tools as Alt. BE Approaches for BCS IV & High-Risk Prods: Generic Industry Perspective**
  Sivacharan Kollipara, MS Head, Biopharmaceutics, Dr. Reddy's Laboratories Ltd., India

- **Advancing IVIVC in Lipid-Based Formulations: Addressing In Vitro Dissolution Challenges for BA Correlations**
- Sandip Tiwari PhD Head of Technical Services, Pharma Solutions, NA, BASF Corporation

- **Enhancing Patient BE Studies Using Model-Integrated Evidence (MIE)**
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Panel Discussion

In addition to moderators and presenters listed above:

Public Panelists:
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Hazem Ali, PhD Senior Chemist, DPQA II, OPQA I, OPQ, CDER, FDA
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Nilufer Tampal: Of the public workshop, I think yesterday was very productive and we heard some stimulating comments and discussions. I think the two sessions that we have planned for today should also be equally thought-provoking and stimulating. I'm Nilufer Tampal. I'm the associate director for scientific quality in the immediate office of Bioequivalence, Office of Generic Drugs. And I'm also the ICH topic lead for FDA's topic lead on the ICH M13A. Along with me, we have Dr. Dongmei Lu, and Dongmei is the acting deputy director for the Division of Therapeutic Performance II in the Office of Research and Standards, Office of Generic Drugs. Both Dongmei and I will be co-moderating the two sessions for the day.

Keeping with the theme of the public workshop, for the first session we will focus on identifying the research to clarify the implementation details of M13A for oral immediate release products. In the afternoon we are going to pivot to modified release products and there we are going to explore the feasibility of the waiver approaches for modified release, and then also consider some challenges with the BE standards set by the FDA for certain modified release criteria. So with that, I'm going to turn it over to Dongmei to start us off with Session 4. Thank you.

Dongmei Lu: Thank you Nilufer. It's my great pleasure to have this opportunity to coordinate this session together with Dr. Nilufer Tampal for sessions 4 and 5 related to IR products and MR drug products. Nilufer already gave some information about the purpose of this workshop. I still want to give a little bit more.

For this meeting, we want to hear from you, the industry and the public, whether there are any identified research gaps in generic drug development. This would help FDA to identify the research and science priorities and the GDUFA commitment. Virtual audience, you can definitely submit your questions and comments during the meeting or even after the meeting. I think the timeline is until July 7th. You can submit your comments at the common docket place for this workshop. The virtual comments will have equal weighting to the comments and suggestions presented at this workshop.

Let's start Session 4. Session 4 is "Implementation of the M13A Guidance: Lessons Learned and Advances for Immediate Release Products". Following the recent publication and implementation of M13A guidance on bioequivalence for IR solid oral dosage forms, we found that there are some significant gaps that persist related to the critical formulations and manufacturer attributes of high risk drug products. This session aims to provide valuable insight into areas that could benefit from further discussion and research, facilitating the successful implementation of M13A for oral IR drug products.

There are also some topics related to M13C preparation. The faculty presentations will focus on the technical and scientific aspects from both regulatory and research perspectives, which can be incorporated into systematic risk analysis for IR drug products. For this session there are two major areas. The first area is challenging and high risk formulation drug products including amorphous solid dispersions and lipid-based formulations as potential alternative BE approaches. The second area is related to modeling and simulation.

Without further ado, now let me give this podium to our first speaker, Mr. Girish Nihalani. Girish is the associate director in product development at Hikma Pharmaceuticals USA, where he leads the formulation development team for development of generic drug and value-added products. He has a specific interest in in vitro-in vivo correlation for BCS class 2 and BCS class

4 drug products. His presentation title is "Amorphous Solid Dispersion Products and Potential Alternative BE Approaches". Thank you for presenting.

Girish Nihalani (Hikma): Good morning, everyone. A little disclaimer, the contents and views presented are not on behalf of any of my present or past employers. Being the first presentation of this session, my presentation will consist of some introduction into amorphous solid dispersion systems - what are the benefits, what are some of the basic aspects, and then looking at amorphous solid dispersions in context with the recently published M13A guidance for bioequivalence of immediate release dosage forms, which takes us to the requirement for alternate BE approaches in order to request for waiver of one of the studies.

Amorphous solid dispersions are single solid-state systems where the API is dispersed at a molecular level in an amorphous form within a carrier system. The benefits are obvious. It helps for enhancement of the solubility and enhanced absorption for BCS class 2 and 4, which produces issues with solubility. In the last two decades, though the concept was invented back in 1961, it's getting more popular due to the increasing surge in BCS class 2 and 4 NCE molecules and the availability of commercially viable technologies. These technologies are also used for 505(b)(2) applications, paragraph 4 certifications, or lifecycle management of an existing product containing a non-ASD API.

Amongst the multiple preparation methods listed in the literature, the commercially viable ones are hot melt extrusion and spray drying. Spray drying is distinguished from hot melt extrusion in that it is a solvent-assisted process that can be carried out at a low temperature, whereas hot melt extrusion requires application of heat and uses heat and high shear to make the drug solubilized within the carrier system.

To obtain a good system, it is very necessary to have a certain degree of solid solubility, miscibility, and kinetic stabilization. The solid solubility refers to the thermodynamic stability of the drug into the carrier system, which is a function of temperature. The miscibility refers to the miscibility of the two amorphous forms under the supercooled liquid state, and the kinetic stabilization refers to maintaining the supersaturated solubility of the drug in ASD or, in other terms, preventing recrystallization over the shelf life.

In this ASD system, if the carrier has functional groups which can act either as a hydrogen bond acceptor or donor for the hydrogen bonds, it's a further added advantage for a very cohesive interaction which further helps in enhancement of the solubility and inhibition of recrystallization on the shelf life.

Some important considerations in the development of ASD involve the selection of the manufacturing process at an early stage. For example, drugs with high melting points or thermal lability are not ideal candidates for hot melt extrusion, whereas spray drying is an expensive process. But the advantage is that most drugs find their solubility in organic solvents and spray drying can be carried out even with a few milligrams of drug substances.

Drug load is an important criteria. In most cases, the polymer required or the carrier required is more than a 1:1 ratio. For high drug loads, sometimes it becomes limited. The technology gets limited due to the size of the dosage forms. Polymer is an important criteria with respect to solubility or miscibility of the drug, which can be modulated by use of other excipients such as surfactants and plasticizers. Most importantly, the favorable outcome - in many cases it is witnessed a perfect ASD may be formed but gets limited by its in vivo performance, the way it acts under fasting and fed conditions due to its dynamic system.

API, drug, and polymer form the heart of this ASD system, whereas plasticizer acts as a catalyst in lowering the glass transition temperature of the polymer, enabling the solubilization of the drug at much lower temperatures. Based on the need, a solubilizer or surfactant is added to achieve the desired dissolution rates.

Hence, looking at the number of factors associated with either composition, which could be related to API properties, polymer properties, or related to the manufacturing process, the equipment design - this all in combination makes ASD a very complex system, difficult to make robust, and challenging. In many cases, at T0 successful ASDs are formed but we have to assure how 100% ASD is maintained throughout the shelf life, as ASD systems are prone to recrystallization under different storage conditions.

Looking at the number of products approved by the FDA between 2012 and 2023, about 48 products are approved which use either spray drying or hot melt extrusion technology. In all these products, this gives a good insight for anyone starting to develop ASD. The takeaway is, analyzing further these 48 products, the ones which use the spray drying process - the carrier system is dominated by the use of hypromellose acetate succinate, whereas in hot melt extrusion, most of the formulations are Copovidone-based, which is a copolymer of povidone and vinyl acetate in a 3:2 ratio.

Hot melt extrusion - I'm not going to go into details. Most of you might have used it or are aware, but the purpose here showing is the number of factors which go into producing an amorphous solid dispersion by hot melt extrusion. Briefly, it consists of feeding a dry mix of carrier system and API along with surfactant which undergo a series of heating zones subjected to high shear and heating. The screw forms the heart of the hot melt extrusion system. During the process, the API undergoes a very intensive shear kneading mechanism in this screw in combination with heat, which makes the API soluble and solubilized in the carrier system. Many of these factors are interdependent on each other, like stability, formation of 100% amorphous, the properties of the extrudate selected. The screw design has a very critical role to play - bilobal versus trilobal, the residence time.

Solid dispersions in context to M13A guidance for bioequivalence of immediate release dosage forms are treated as complex dosage forms because food is known to affect the solubilization of the drug, and this becomes more pronounced if it is affected by performance-enhancing characteristics of the amorphous solid dispersion. The amorphous solid dispersion is complex and variable from product to product, manufacturer to manufacturer in terms of its composition and also the technology used. Hence, the food effect on these systems is variable and difficult to assess. That is the reason it is treated as a complex system under the purview of M13A guidance and is required to meet both fasting and fed condition bioequivalence studies. However, as ASD is still under development, the agency is open for discussion from case to case if a waiver for one study can be justified based on alternate approaches.

Hence, this M13A requirement of both studies, fasting and fed, takes us to more research work on alternate approaches. There are multiple modeling approaches, modeling systems reported in the literature. And maybe some of those will be presented by the speakers. There are two of these I would like to highlight, which are good research conducted at University of Maryland and Institute of Frankfurt, which is sponsored by FDA. One system was an in vitro lipid lipolysis-based system which was based on the concept that partially hydrolyzed lipids help in solubilization of BCS class 2 drugs. So lipolysis media were developed. Different drug products containing low solubility drugs - rivaroxaban, itraconazole and ritonavir - were studied. In case of

rivaroxaban, different strengths were studied. The 2.5 and 10 mg are not reported to have food effect and 20 milligram is reported to have food effect. When I say food effect, it means the higher PK parameters compared to the fasting state. For itraconazole, the effects are formulation dependent. The Sporanox and Sempera have ASD formulations based on HPMC system, whereas the Tolsura is based on HPMCAS. Sporanox and Sempera reported a positive food effect, whereas Tolsura is reported to have a negative food effect. For both rivaroxaban and itraconazole, the in vitro lipid lipolysis model was in agreement with the reported PK data, whereas in case of ritonavir formulation, it is reported to have a negative food effect. But the model is still predicting a positive food effect. Hence, we require further research case to case, and this itself is exemplified like even studying the ASD formulations from different manufacturers - they do not present the same food effect.

Another such modeling system is a physiologically based biopharmaceutics modeling system, which integrates the intensive characterization involving the solubility study of API and drug product in multimedia and biorelevant media, plus the dissolution in biorelevant media under fasting and fed conditions. For the fasting, a 2-stage pH shift was mimicked as if in pH increment like from pH 1.6 to 6.5, whereas in fed, a 3-stage pH shift - the pH for simulated gastric fluid to low pH. And all that in vitro dissolution media data was fed into the software GastroPlus with the in vitro characterization tool along with the biopharmaceutic properties of the drug like LogP, molecular weight, etc. And that integrated simulated model predicted was validated and was in agreement with the in vivo reported PK data of Sempera and Tolsura, which contains itraconazole in the ASD form. Sempera contains HPMC-based polymer (pH independent), whereas Tolsura contains ASD in HPMCAS, which is pH dependent. Hence Tolsura has a negative food effect compared to Sempera which has a positive food effect.

There are more models reported in the literature, which are based on GastroPlus models, compartment models, reports of organ-on-a-chip, use of artificial intelligence - the list goes long and some of these are presented by the speakers. The question is, there is not a universal or harmonized workflow to predict - one model will not suit the need for all molecules in general for BCS class 2 and 4, and hence more research is needed in these areas.

Putting some of my thoughts here based on understanding of ASD and the M13A guidance - what could be the potential or alternate BE approaches one can approach? Which can - one approach which we can think of is like a solubility analysis from the ASD system. So it is highly likely this may not behave like a BCS class 2 or 4, not necessarily. One can argue based on the different food effects and one can support based on the therapeutic index of the drug. The in-depth - some in vitro and in vivo - not necessarily correlation, but at least what we call in vitro-in vivo extrapolation models and approach agency to see if a waiver can be granted for ASD systems. The reason M13A requests to conduct fasting and fed study for ASD is because of the differences in the performance-enhancing characteristics of the composition from manufacturer A to B, composition A to B, or technology A to B. So for the molecules which can be qualitatively similar to innovator product and maybe quantitatively reverse engineered, one can adopt these approaches.

So overall, knowing how the ASDs are formed, the factors that go into the formation of ASD, the multiple factors affecting related to composition, process makes ASD as a whole very complex and under the purview of M13A, requires to have both fasting and fed study as of now. More research has to be done to support waiver for either of the one study. Some of the model and simulated-based approaches will be described later. With that, I would like to thank whoever has supported me in this. Thank you so much.

Dongmei Lu: Thank you very much Girish for the wonderful presentation. Our next presentation is from Dr. Geoff G. Z. Zhang. Geoff is the founder and chief technical director of ProPhysPharm LLC. He has contributed broadly to physical pharmacy, specifically in the areas of salt and polymorph screening, co-crystallization and crystal engineering, characterization and crystallization of amorphous solids, physical properties of supersaturated solutions, and design of amorphous solid dispersions. His presentation title is "Dissolution of PVP-VA Based Amorphous Solid Dispersions and Absorption of Poorly Soluble Drugs". Dr. Zhang, please.

Geoff G. Z. Zhang (ProPhysPharm): Thank you for the introduction and invitation. I'm going to take a little bit different approach. Most of this work was done with Lynne Taylor over at Purdue University over the last 10-15 years. We've formed some opinions and have some data to show to sort of look at the dissolution mechanism. I'm going to skip some of the introduction slides because it's covered in the previous presentation.

Starting right here. So in the framework of solubility, you can have some kind of mental exercise. What makes a solid soluble in water? So imagine you take a molecule from a crystal lattice where you have a penalty for lattice energy, and you create a void in the solvent that can accommodate this molecule. That's two different steps. In the first step you pay a penalty and then you put a molecule in there and that's where you get the interaction back and you basically - the overall balance of three factors gives you the solubility. So this is the case for crystalline material. If you go to amorphous, the only difference is the first step where you don't have to overcome the crystal lattice energy. Instead, you just take a molecule from the liquid. That's the amorphous phase. So you pay much less. Therefore, the amorphous solubility is much higher than the crystalline material.

So qualitatively you can express the ratio of solubility in amorphous with this equation. The first term is actually the free energy difference between the dry amorphous material and the crystalline material. You can calculate that based on the melting point, heat of enthalpy. And the second term is really a correction factor where because the amorphous phase basically is a liquid, it will take up water. And when you have water going into the dry amorphous stage, you inevitably go from a single liquid to a mixture of liquids. Therefore you decrease the activity. And basically drop the solubility. So after you've done that, we look at the correlation between the prediction from this equation and the actual measurement. It looks like over about 12 to 18 systems, it looks pretty good correlation.

So amorphous is a whole lot more soluble than the crystalline phase. So we try to take advantage of that and design amorphous formulations and from the solubility here you can see it translates to dissolution rate. So here is the intrinsic dissolution rate of amorphous and crystalline ritonavir. And you can see it is about 10-fold increase. That's great. And this dissolution difference also sort of translates to the absorption in animal. So here on the right is the exposure in rat of different solid dispersions compared to the crystalline and there you get almost 20% to 24% increase in exposure. So we see that amorphous is highly soluble, much more soluble than the crystalline, and dissolves faster and it gets absorbed in the animal better. So that's the sort of the driving force why we look at amorphous solid dispersion more widely.

But in reality, we find out that the actual dissolution of ASD is much, much faster than the amorphous material. So here is the dissolution rate of again amorphous ritonavir. This time it's at pH 6.8. So it's dissolving, but it's very slow. It's one microgram per minute dissolution rate and compared to the ASDs, you can see the dissolution is so much faster than the amorphous dissolution rate. And interestingly, the different drug loadings are - they pretty much released at the same rate. So if you compare the dissolution rate of the ASD and the amorphous ritonavir,

it's about a 400 to 800 fold increase. Beyond the amorphous. OK, so we start asking question why?

What we find out is that at low drug loading where you have very high release of ritonavir, your drug and polymer they are releasing at the same pace. These are the two bars comparison. But as you go to higher drug loading where the release rate is very slow, you're pretty much not going out. It's like a pure amorphous ritonavir. So we had some additional study on the surface of those dissolving tablets and we find out that at high drug loading, the surface is covered with pure amorphous ritonavir. And we know that ritonavir, even though it's amorphous compared to ASD, the dissolution is terrible.

OK, so based on this series of study, we put a concept out there. It's called a limit of concurrency. So basically it's the highest concentration, highest drug loading that you can have where your release of the drug is controlled by the polymer and the drug and the polymer they are releasing at the same pace. And from that point of view, it's normal to choose that as your drug loading, right? Because once you exceed that, your tablet is not going to dissolve. OK. That's the ritonavir system and we look broadly over a whole bunch of different drugs and I'm just giving you one example that's related to sofosbuvir that's in the HCV product from Gilead. And it also has the same behavior and the LC as opposed to that's around 25%. This drops to 5%. OK.

And we look at what can impact on the limited concurrency or drug loading and what we find out is that a small amount of surfactant - here is about 5% - can drastically change the behavior. So now we are at a 30% drug loading. This over the LC of ritonavir. Some works great, some does not. OK. And we also - well again for sofosbuvir, if you incorporate a very small amount of 5% in the formulation, you can increase the LC from 5% all the way to 30% - a six fold increase. So that's a common thing that people use in the formulation that's affected. What we find out is that even some other excipient plasticizer is usually to decrease the TG to make extrusion better, they also increase the LC or drug loading, sometimes 5%, 5 fold increase. So a very small amount of excipient that's present in the formulation can have a huge impact on the dissolution.

And we know why that happened. Is that when it dissolves very fast and bring drug into the apex, they phase separate. They form particles of pretty much drug and suspension in the aqueous medium. OK and those droplets usually very small in size and because of that whatever formulation that you use to enhance the dissolution rate will end up - if you do it good. OK, if you do it really well, you can reach the amorphous solubility and create those droplets. But the concentration, the free concentration of the drug will not increase any further. That's just a physical chemistry of insoluble compounds. But there's still benefit for those droplets. OK. What happening is that they present there as a reservoir for drug because of their huge surface area. Because the particles are usually in the nanometer range, they feed into the aqueous really fast. OK. So if somehow you are removing the drug, let's say absorption, they can maintain the concentration in the aqueous, therefore sustain the absorption over time.

So here is our view of the GI tract which looks funny, but we think in the GI tract the aqueous compound is pretty much the central compound that interacts with the membrane and where the absorption occurs. That's the mass transfer path. But there are a lot of peripheral compartments in the GI tract, so it can either be crystals. OK. It's a recrystallized or complexes. Or the amorphous in the droplets that is formed and you have surfactant in the GI tract in formation, they interact with the central compartment with different rates. OK. So when the drug is being absorbed, they feed into the aqueous and sustain the absorption over time.

So beyond the release and generation of those droplets, there are several more critical points. That's afterwards - one is the different formulation. When they do have a good release and it's below the LC, they generate the droplets. What's the size of those droplets as a function of formulation? Here we show several different effects and that's included in the ASD, when they dissolve and generate nanoparticles, they have very different particle size and if you have a very good surfactant there, you have 50 nanometer droplets. OK, if you don't have surfactant, that's 250. So that's a 5 fold difference in particle size and counts of droplets in the GI tract. That obviously will impact on the absorption.

And also once those droplets are formed, are they stable? OK, in order for them to work really well, they need to stay as nanoparticles and feed into the aqueous phase. But if they coalesce or they agglomerate, the effective surface area is lost. Therefore it's not going to work. So another important factor is the physical stability of those droplets, and you can see that the polymers - through impact on that? Oh, that's the impact. In order to stabilize and keep those nanoparticles nano, usually you want polymers. But naturally, if you put a polymer on the surface of the solid, that will slow down the mass transfer. So we have data to show that under certain conditions, different polymers and at different polymer concentrations do impact on the dissolution rate from the amorphous phase, which means the feeding of the aqueous will not be the same. So there are a lot of tradeoffs.

So couple of these together, there are four different aspects that we need to consider in order for a good formulation to absorb well. So going from the number one point here is the release aspect. That's where we did the most study. The second is physical stability. On the formulation component and the third is figure stability, stability and at the last is actually the dissolution rate of the amorphous phase.

So the question is, what actually do I - oh. The going to the depression that - that all the gap that we have is yes we in vitro we demonstrate the benefit everything about the nanoparticles, but in vivo, does it really matter in order to have good absorption. Do you really really have to have those really small nanoparticles that form during the dissolution of your formulation? In vivo. So we have some evidence here. Here is a study we did in the rat. OK on the right, on top. There, these are the ones that generate the nanoparticles and the activity of the system is is the highest it can be. On the bottom left here, these are the crystalline or the ASD formulation that actually crystallize when it comes in contact with water. So they are low, OK. And there's one that couple of them in in the middle, that's those are the ones that did not generate nanoparticles, but they are super saturated. So they they create concentration upon dissolution, that's beyond the crystalline solubility, but did not reach amorphological solubility. So from that it looks like there is a pretty good trend there. OK, higher activity is better. And it is the best when you are able to generate nanoparticles.

So that's one study. There's another study that's done by Merck. They actually purposely generate those nanoparticles with different sizes. So on this plot. Y-axis. It's exposure. X-axis is the particle size of the droplet. And they create those droplets. They dose the animal with the droplets with everything control, so the actual suspension has the exact chemical composition. The only difference is the droplet size. OK. There you can see that when you when you go down in your droplet size, your exposure increases, but it may not increase please, until you reach small enough particle size. So these are the studies that actually sort of telling us the nanoparticle is really helping in absorption. But the question is these are done in animal. In human. Is it really required? Although we have many products, but we've never done systematic study for mechanistic understanding.

So here's the question is that is it possible that we can do similar study in human to really understand the need for those droplets? Cause, the other thing. I think that's a gap and it's impacting on absorption is the in vitro in vivo difference. We do experiment the best we can and we use simulated fluid. OK, so we take a biorelevant, put it in the buffer and it will do it in the - but in reality, in our human body, we have all these biosurfactants in the body with different composition. So we took only this STC, this one into the simulated fluid that we used in the lab. So we did a study. We actually mix up all these biosurfactants with the right average composition in human and we look at how is that different from the simulated fluid we are using now in the lab. Here we have crystalline solubility for some system. It's not really changing some different for amorphous the same same story. So depending on the system your real GI tract fluid could be very different from from the simulated fluid we use to assess formulation in the lab. OK. This is the solubility aspect.

We also look at the crystallization aspect because there are papers published out there demonstrating that some of the biosurfactants has a good crystallization inhibition property. So we look at the crystallization inhibition. Comparing the simulated fluid we use in the lab and the composite SIF that we prepare. And you can see that the induction time for the different system, there's some has no impact. Some has a great impact. So based on this we I think there there is a difference in medium when we do things in the lab. OK, we see the behavior, but the same behavior may not replicate in our human GI tract, and that that's a difficult situation for us. How we supposed to understand our formulation, where we're doing things differently than our body. Of course, agitation is a little bit different. In order to do the experiment well and with low standard error, good data, we need to stir, agitate and make it reproducible. But in our human body it's not being stirred that much. So that's another difference, I think though one of the biggest difference, especially for those that crystallize really easily is the one that in the lab is a closed system. Whatever dissolve is there, but in the body it's open system. Things are being absorbed, so if it's crystallizing in the body, it may not crystallize that easily.

So these are some of the things I think we need to continue to work on and understand better. So I think I just leave it here. Any questions? I have 16 seconds.

Dongmei Lu: So yeah, we will leave the question until the panel discussion, OK.

Thank you very much, Dr. Zhang for the very informative information about the ASD. And also next presentation is from Mr. Sivacharan Kollipara. He is going to present virtually. Hi Siva.

Sivacharan Kollipara (Dr. Reddy's): Hello.

Dongmei Lu: OK. Yup. So Siva is the head of biopharmaceutics in Dr. Reddy's Laboratories in India. He is responsible for the biopharmaceutics evaluation, bioequivalence risk assessment and bioequivalence prediction for conventional as well as complex generic drug products. He's also involved in the PK modeling and simulation activities supporting generic drug development of various immediate release, modified release and complex drug products. He also is involved in utilizing non-compartmental PK and PBPK and PBBM modeling approaches for regulatory justification for various markets. And so Siva, please take it away.

Sivacharan Kollipara: Thank you. Am I clearly visible and audible? Can anyone confirm please? Am I audible and visible?

Dongmei Lu: We can hear you, yeah.

Sivacharan Kollipara: OK. Can I take the control of the stage and present slides from my end? Can I take the control of the stage and present the slides from my end? If it is OK?

Sheldon Thwaites: Yes, yes you can.

Sivacharan Kollipara: Alright, so let me just share my screen and please see if you can see my slides. All right. Thank you so much for the introduction as well as the invitation. Today I'm going to talk about use of modeling and simulation tools as alternative bioequivalence approaches for BCS Class 4 molecules containing drug products as well as the high risk products. I'm going to give few perspectives from the generic product development. I would like to start with a disclaimer. The contents of this presentation represents the opinions of myself and they do not represent that of my company.

So the content of the presentation is like this. First, I'm going to talk about generic industry perspective, opportunities and challenges on ICH M13A guidance followed by some bit of detail into high risk products. And then I'm going to talk a little more detail about alternative BE approaches, which is the PBPK modeling followed by two case examples and then I'm going to talk about the potential research areas and directions in these aspects.

So starting with the generic industry overview of the M13A guidance, M13A guidance is a harmonized guidance and which has led to harmonization of the bioequivalence requirements across the geographies and it has provided a lot of clarity with respect to bioequivalence requirements for high risk and low risk products and in addition it also has detailed various aspects with respect to study design as well as study conduct. It has provided a lot of opportunities in terms of reduction of the BE burden on the generic industry wherein triple comparator products can be included in the same study and with respect to US FDA as well. Now the synchronization of guidance is as per the label recommendation. And also depending on the complexity of the drug product, we're also eagerly looking forward for M13B, which is already in the draft stage and it has given lot of clarity with respect to dissolution similarity and formulation proportionality and also looking forward for the M13C guidance that is going to detail about highly variable drugs and NTI bioequivalence requirements.

So moving on to the high risk products, as per M13A, all of the previous speakers have talked in detail about the ASDs and the complex products and the requirements of both fasting and fed bioequivalence studies and in general, the complex products are high risk products. As per the guidance, consists of solid dispersions, microemulsions, coprocessed APIs and in general it is very difficult to extrapolate the behavior of these formulations from fasting to fed condition or vice versa, and that's where both the studies are in general recommended. Within the amorphous solid dispersions, the exposure depends on the type of polymer which has been used, as well as the manufacturing process and within the lipid based formulations. Again, they can range from different types of formulations depending on the type of oil and the surfactant. It can - that has been used in the formulation and they can also undergo complex absorption pathways like digestion and lymphatic absorption. Within the nano formulation, again, the rate of absorption depends on the size of the formulation or the size of the API that has been present. And presence of alternative excipients which are present in the nano formulation can also make the prediction of the absorption difficult under the fasting and fed conditions. And that is the reason why these high risk products require fasting and fed BE.

And this slide is going to talk a little more detail on that. Coming to the amorphous formulations, if the test and reference formulations are different with respect to the composition or the type of polymer used, especially with regard to pH independent or pH dependent polymers, which can

cause different extents of solubilization leading to difference in the exposures in fasting and fed condition. And IVIVC is also challenging for this formulation. And most of the times, dissolution may not be able to predict the in vivo performance and we need to delve into a lot of depth to understand what is causing the in vivo expression.

Within the lipid based formulations, if it is a simple oil based formulation then it can have lesser dispersion, but the moment we try to add some oils and surfactant and co-solvents it can cause a different in vivo behavior. And that's where this also becomes difficult on the in vivo prediction perspective. In case of nano formulations, depending on the size of the API that has been present, it can cause different extents of solubilization in fasting and fed condition, and there can also be a presence of alternative absorption such as paracellular, which becomes evident especially when we reduce the particle size significantly. So because of the challenges associated with these formulations in terms of exposure under the fasting and fed conditions, prediction of exposures in one of the conditions becomes very difficult and that's where both fasting and fed bioequivalence studies are suggested for high risk products.

So in this table I just compiled the formulation principle as well as extent of food effect that has been observed for different formulations collected from the literature. For the first case, solid dispersion as well as spray dried formulation, they have given different extents of food effect and in itraconazole example also has been highlighted by Girish wherein the type of formulation which has been used has caused the food effect in different direction. Hypromellose based ASDs have caused positive food effect, whereas HPMCAS based formulations have caused negative food effect. Similarly, we do also see the difference in the extent of food effect between immediate release and extended release formulations and within the immediate release formulations as well. Depending on the formulation principle which has been used, we see a difference in terms of the food effect and because of this, just to sum it up with the learnings from the previous slide, it is a little difficult to extrapolate the bioequivalence requirements in fasting condition to fed condition, and that's where both fasting and fed bioequivalence studies are required typically for these formulations.

So now just as a food for thought, can we get a waiver for one of the bioequivalence studies either fasting or fed condition in these specific type of formulations? So let us take a case scenario where an amorphous solid dispersion or a lipid based formulation - it has Q1/Q2 similarity with the innovator composition and both of them have been manufactured using the same manufacturing process and both of the formulations have similar grades of excipients. So in such case when there is equivalency existing between innovator as well as generic formulation, can we do a detailed biopharmaceutic risk assessment to ensure the similarity in the solubility as well as the kinetic solubility and the dissolution in multimedia conditions followed by the physiological based models to ensure the equivalency of both of these formulations in one of the conditions and can we get a waiver of either fasting or fed study? This is just a food for thought.

Now moving to the later part of the presentation, which is talking about the use of modeling and simulation approaches as alternative BE approaches for the high risk products. Applications of PBPK and PBBM - I think everyone is aware there is a lot of emphasis in the recent times because of their potential to waive off certain clinical studies. And especially in the context of the generic product development, PBPK and PBBM have demonstrated their superiority in terms of superseding the dissolution similarity, dissolution specification justification, assessing the bioequivalence between reference and test product using the virtual bioequivalence or clinically relevant dissolution and complex BE studies waivers, especially in the context of fed

bioequivalence or PPI drug interaction studies. We are going to spend some more time on these study waivers to understand the use of these tools as alternative BE approaches.

So how do you develop a physiological model for the high risk products? What are those modeling inputs? Typically, the physiological based models can be divided into 3 categories, so you can have an absorption model, you can have a physiological model and you can have a disposition model. So physiological models are basically talking about the physiology, the gastrointestinal pH, blood flow, transit times, emptying rates, which typically vary between fasting and fed conditions. So most of the software platforms for PBPK and PBBM, they have embedded physiological models. Then coming to the disposition model, which basically uses the inputs of protein binding, blood-to-plasma ratio and defining the elimination kinetics which can be depicted in the model through compartmental as well as based on the enzyme or transporter Vmax and Km or the Michaelis-Menten kinetics.

The major focus in terms of high risk products waivers comes from the absorption model. Because the solubility as well as the dissolution rate are going to govern the in vivo behavior under the fasting and fed conditions for this type of formulations. For amorphous formulations, kinetic solubility, the dissolution in biorelevant media, supersaturation solubility, precipitation kinetics, and the transfer experiments data can be used. In case of microemulsions, again, we can use the kinetic solubility, the dissolution in the media and typically the presence of lipids as well as surfactants can enhance the solubility so that solubility enhancement factor can be used coupled with specific data coming from in vitro digestion. I think the subsequent speaker is going to cover a lot about the digestion and other aspects. When it comes to nano formulation, typical inputs will be solubility enhancement factor coupled with particle size and dissolution rate enhancement.

So once the PBPK model or PBBM is developed with all the set of parameters, the model validation can be conducted using the virtual BE wherein the model can be validated with the reported food effect or across the doses and in addition parametric sensitivity analysis can be performed to understand the specific parameter which is sensitive to the in vivo performance. Followed by that, the model can be applied using virtual bioequivalence to predict the performance under the fed BE conditions and totally a validated model with the different formulations, different doses can be used to obtain the waiver in one of the conditions for the high risk products.

So talking little more specifically about the model inputs for the high risk formulations, they can be categorized into dissolution based models, dissolution based inputs, solubility related as well as other specific inputs. So in terms of the dissolution, two stage dissolution, which is taking care of the precipitation or the biorelevant dissolution, multimedia dissolutions and especially for the ASD formulations, the formulations which have been manufactured with different crystallinity to understand the sensitivity of the dissolution towards the crystallinity also can be utilized in the model. In terms of solubility, typically conventional or saturation solubility is used in the models, but for formulations like amorphous solid dispersions kinetic solubility wherein the solubility is determined across the time points and in correlate the time point corresponding to the Tmax of the formulation can be used in the model. And in addition, the solubility in fasted as well as fed intestinal fluids also can be used. In terms of other inputs, as and when it is applicable, the particle size, mean precipitation time and digestion data also can be used in the model.

Recently there also have been a lot of emphasis on the data coming from complex systems because these systems are closer to the in vivo scenario. For example, the data coming from TNO TIM Multicompartment Dissolution systems also can be used. And the artificial stomach

models also can be used as they take care of the precipitation and specialized approaches like dissolution and permeation system, wherein the dissolution analysis is also combined with the permeability estimations can also be inputted into the model for accurate prediction of in vivo behavior.

Although we understand the potential of these models, that comes with a little bit of challenges, especially for high risk products, because in terms of the validation of this model we can firstly validate these models with the conventional formulation data, literature data. For example, you have the data for different doses or different dosage forms, and fasting and fed condition or the PPI. All of this data can be used for the validation and the validation can also happen to predict the food effect accurately. And if you have the data coming from pilot and pivotal studies with the help of virtual BE, the models can be appropriately validated and similar is the case for the PPI. And further, we can also do the parametric sensitivity analysis to understand the parameter which is causing the impact on the in vivo performance. And of course all of this validation can also be coupled with the detailed biopharmaceutical risk assessment to make the case much stronger.

However, there are few challenges to apply the PBBM because as we have seen from the previous presentations and also from the literature, IVIVC is not always evident for the amorphous solid dispersion formulations. Dissolution or solubility may not govern. Specific in vitro tests might be required and you need to identify what is the test which is accurately depicting the in vivo behavior and the case becomes a little more complicated whenever you have non-Q1/Q2 formulations which are used in the ASD. It's very difficult to understand what is that factor that is governing the in vivo behavior.

So, having understood the basics of PBBM and PBPK in high risk formulations, let us also try to talk a little bit more about the lipid based formulations. In the lipid based formulations, unlike the conventional formulations, there will be specific pathways with respect to lipid digestion followed by the absorption and thus the IVIVC may not be really straightforward. However, few attempts have been made in the literature wherein the dissolution is correlated with the in vivo performance. The dispersion of the precipitation kinetics also can be correlated and the specific phenomena that the lipid based formulations undergo, which is the lipolysis or the lipid digestion. The data coming from this in terms of the percentage drug that is available as a solubilized fraction after the digestion can be used and sometimes the in vitro performance also can be correlated with the ex vivo permeability studies coming from everted sac models, so some of these specific tools can also be used for establishing IVIVC for lipid based formulations.

So with this I would like to talk a little bit into depth of PBBM and PBPK in obtaining the waivers for complex formulations using the PBPK methodology. The first case study talks about the role of modeling approaches in obtaining the fed bioequivalence study waivers. So before we apply any model for bioequivalence prediction, either in the fasting or fed conditions, it is important to establish the biopredictive dissolution. The biopredictive dissolution is something that can provide a quantitative information about performance. So for the fed conditions, although we use biorelevant fed state simulated intestinal fluid for solid dosage forms, typically we also found that simple media with surfactants or the two stage dissolutions can also provide an information about in vivo performance.

So once you have the data generated in these dissolutions and once you have the pilot bioequivalence information available, you try to correlate the observed bioequivalence data against the dissolution behavior. If there is optimization of the biopredictive media required, we can do that and further the biopredictive dissolution ability to predict the in vivo performance can

be quantified using subsequent pilot studies as well as pivotal studies. And this is the flow chart which we can follow for the development of appropriate biopredictive media, especially under the fed condition.

What we also have done is that we have taken approximately 36 case studies where we have applied PBBM to predict the food effect accurately and we try to understand the correlation of various factors which is causing successful prediction by using PBBM. So we categorize the factors into BCS class and the type of food effect and the type of formulation - immediate release, extended release - and what we found is that within BCS class molecules, BCS Class 1 exhibiting high solubility, high permeability or BCS class 4 molecules which is showing the enhanced dissolution in solubility rate, the food effect of these formulations can be predicted accurately and the positive food effect also can be predicted accurately. In contrast to the negative food effect and immediate release formulations, food effect as well as the extended release formulations, which are manufactured with BCS class 1, the food effect can be predicted accurately. When it comes to the mechanism of action, if the mechanism of food effect is coming because of the enhanced solubility or dissolution rate, those cases can be accurately predicted by the model, and if it is a negative food effect, we need to understand the exact mechanism which is causing the negative food effect. Then we can predict the food effect using the PBPK model.

So here is the case study for waiver of the food effect fed bioequivalence study for complex formulation. Reference product has a micronized API whereas a test formulation is a solid dispersion and we have conducted the pivotal fasting bioequivalence study and for the waiver of the fed study we have used the PBBM approach. So in this case the model has been developed through integration of all physicochemical properties and the virtual bioequivalence has been carried out using the fasted bioequivalence data. And with appropriate inputs of dissolution and solubility, we have predicted the performance under the fed condition and the virtual bioequivalence has indicated successful bioequivalence under the fed condition with the appropriate inputs. The in vivo dissolution also indicated that there is no difference between the fasting and fed state between the reference and test formulations under the fed condition. To supplement the data from the modeling, we also have done significant amount of biopharmaceutical risk assessment where we justified the waiver of the fed study with the help of general biopharmaceutic properties in comparison of compositions of test and reference formulation, together with the multimedia dissolution. The PBBM coupled with the biopharmaceutical risk assessment has resulted in fed bioequivalence study waiver and agency has accepted this particular application.

The second case study is with respect to reformulation of BCS class 4 molecules to avoid the repeated bioequivalence study. So this is specially with respect to the excipients formulation in the drug product and how can you use the PBPK approach to avoid the bioequivalence for reformulated drug products in case of BCS Class 4. BCS class 4 molecules are a little bit different as compared to other classes because their in vivo exposure is subjected to solubility as well as the permeability changes. So for this purpose we have selected couple of molecules and I'm going to talk about one of the molecules in the present case study.

So the molecule we have selected in this case is which is a BCS class 4 molecule. And there is involvement of P-gp in the disposition, and P-gp is again very notorious and any solubility changes, dissolution changes or permeability changes, it may lead to bioinequivalence. So in this case we have developed the model appropriately. It has been validated against the clinical data and then subsequently the model was applied to understand the impact of permeability changes, P-gp kinetics changes which can happen in presence of alternative excipients which is

used in the reformulation. The model has been developed across the oral doses and we can see that the prediction errors are acceptable in this case. And subsequently we have performed the parametric sensitivity analysis with respect to Vmax and Km of P-gp for AUC and Cmax in conjunction with the permeability.

So this approach has told us that any excipient that is altering the Vmax or Km may not have significant impact on the in vivo behavior. But if any excipient is altering the permeability, it is going to lead to bioinequivalence and the permeability safe space also has been defined in this particular case, wherein any excipient causing the permeability alterations beyond ±10% has definitely is going to lead to the bioinequivalence. So this case example highlights that in case of reformulation, any excipient that has been added, which is causing the alteration in the permeability is going to have impact on the in vivo performance.

As I mentioned previously, BCS class 4 molecules are also sensitive towards the dissolution or the solubility, not only the permeability. So for this case, in order to understand the sensitivity of the model with respect to dissolution rate, we have virtually developed different formulations with a range of ±10% or 20% dissolution rate. What we found is that any excipient that is causing the difference of -20% is definitely going to lead to bioinequivalence. So overall, the approach which has been portrayed in this case for BCS class 4 molecules indicates that we need to take care of any excipient that is causing the permeability alterations or the solubility dissolution. And PBPK modeling can be successfully used to assess the impact of reformulation and potentially can avoid the study.

So with this I would like to propose a few topics for research in the future, especially for the complex products development of in vitro methods which can simulate the in vivo behavior. And there also has been increased research with respect to in vitro systems which are more complex in vivo performance and we also need to look into the tests which are other than dissolution, for example kinetic solubility or supersaturation assay. The droplet size which the previous speaker is also mentioning are important. We also need to focus on validation approaches for PBPK and PBBM models, especially for the high risk populations. And apart from the PBPK models, emphasis also can be put on the biopharmaceutic risk assessment in order to get a specific waiver for the high risk products.

So the conclusions - we have seen that PBPK models for high risk molecules with specific inputs with respect to solubility, dissolution and accounting for the specific type of food effect are the in vivo mechanism can be attractive choices and we also need to look into some other ingredients other than in vitro dissolution, which can provide more understanding into the ingredient, and PBPK and PBBM continues to evolve as alternate to BE approaches for high risk molecules. And knowledge sharing in the conferences or workshops like this definitely facilitate more understanding in this direction.

With this, I would like to thank my colleagues at Dr. Reddy's and the cross functional teams who have contributed to this case studies and I also would like to thank US FDA for giving me this opportunity to share my thoughts in this workshop. Thank you very much.

Dongmei Lu: Thank you very much Siva for the nice presentation. So our next presentation is from Dr. Sandip Tiwari and Sandip is the head of technical services and pharma solutions in BASF Corporation. He has over 25 years of experience in formulation design, scale-up and commercialization of complex drug products and his presentation title is right here is "Advancing IVIVC in Lipid-Based Formulations: Addressing the In Vitro Dissolution Challenges for Bioavailability Correlations". Thank you, Dongmei, and thank you FDA for inviting us.

Sandip Tiwari (BASF): The topic of my discussion today is advancing IVIVC in lipid-based formulations addressing in vitro dissolution challenges for BA correlations. If you look at M13A, the guidance M13A, you know it outlines the bioequivalence requirements for immediate release dosage forms and as Siva very nicely explained in his presentation, for most of the immediate release products you know fasting state study may suffice. However, for complex drug products, you know like amorphous solid dispersions, or lipid based systems, there is a need to do fasting and fed studies. So that creates a barrier, in fact for not only the implementation, but also the introduction of generic drugs over a period of time.

So it was - it is an attempt, you know on our side to see if you could at least develop or explore some tools that could be used for predicting the behavior of these complex drug products in vitro that would mimic in vivo performance. And this is one such attempt in our study. The agenda for this session are - my slides will include very brief introduction to lipid based systems, not going into the details, the reason for their complexity, what are the challenges in their dissolution performance in vitro and why it cannot be correlated to in vivo performance, and a tool which we are exploring at our end which is based on dissolution and permeability model, some case studies with that model and then finally looking at the challenges with that model, what are the current challenges in implementation of that model and that could form in fact the basis of research going further in this area.

Now if you look at lipid based systems, you know most of the lipid based systems are self-emulsifying drug delivery systems. You would also hear the name self-nano-emulsifying drug delivery systems or self-micro-emulsifying drug delivery systems. They're all but the same. The difference is that the globule size of the emulsion droplets that you get varies either to nanometer level or to a micron level. That is the only difference.

So if you look at self-emulsifying drug delivery systems, it's a very interesting topic. It's very complex, but at the same time very interesting and there is a paradox also here. If you look at self-emulsifying drug delivery systems, these drug delivery systems are the systems which emulsify or self-emulsify upon contact with gastrointestinal fluids. And then you know, these emulsion droplets are then digested. They are digested. Either they are partitioned into the membrane or that also enzymatically chewed, you know, to release the drug. And this is very interesting. If you look at the definition, you know the SEDDS are comprised of oil, surfactant and a co-surfactant. So they are anhydrous actually, by nature it's very interesting. They're anhydrous, however, when they self-emulsify, when they come in contact with aqueous fluids in gastrointestinal tract, what they form is not an oil-in-water emulsion or water-in-oil emulsion, but rather an isotropic continuous microemulsion. It means it is thermodynamically stable and optically clear solution and this is very interesting, even though SEDDS are not oil-in-water or water-in-oil emulsions, they do form a continuous bicontinuous phase. It means that there is - there is a continuous oil as well as water interface, you know in these systems and this is very interesting and that's why these systems typically require surfactants which have high HLB as well as low HLB. So that when they emulsify in GI, they are able to incorporate the aqueous component as well to make them thermodynamically stable.

As I was talking earlier, typically the primary surfactant here has an HLB - HLB which is greater than 10, whereas co-surfactant typically has HLB of less than 10. And you know, there are some examples here for those surfactants which are shown and which could be used for formulating these systems. It's very interesting, you know, as Siva was also mentioning the self-emulsifying drug delivery systems are complicated. They're complicated also because of the way they interact. As I was explaining earlier, they are digested and the API is released and absorbed and

the way it is done is - the way it happens is that either they're partitioned into the gastrointestinal membrane or they're digestive enzymatically chewed. And I think what is interesting here and why they are complex is that the mere fact that they are made up of oils and oils are nothing but fatty acids. And, you know, fatty acid chains, you know, different composition and that composition could vary from batch to batch and also these systems are dynamic. You know dynamic means when there is a formation of these microemulsion droplets you know they could change their size, you know, dynamically, you know, over a period of time. And that's why and you know, depending on that, their digestibility could also vary.

You'll see that based on the composition of the oils used, you know if you for example if you use long chain lipids you know they will have low digestibility. At the same time if you use short chain lipids they will have high digestibility. Similarly, saturated chains you know saturated could lead chains could lead to low digestibility, whereas unsaturated chain lipids could lead to high digestibility, high surfactant concentration obviously will lead to low digestibility and high oil content could in fact lead to higher digestibility. I think you know this is self-explanatory. There are examples of the oils you know, for example low digestible is Kolliphor RH40 whereas high digestible is Capmul MCM and again you will see that you know the size and the digestibility is also modulated by the oil phase, the surfactant type and API concentration and potential for recrystallization into this system.

So if you see in the literature, typically the self-emulsifying systems are classified into four classes, you know, in fact 5 considering A and B classification. However, at BASF, we are trying to classify them based on their digestibility and also hydrophilicity or hydrophobicity into the four classes. The 4th one on the top right really is not stable or practically possible. So typically we consider there are three types you know based on digestibility as well as hydrophilicity and on the right hand side, you know here you will see this is a pictorial representation of the globule size which is typically in the range of nanometer. And this is a reference 30 nanometer droplet size. So you'll see that the compositions, you know what you see here out of the ten SEDDS compositions which we have proposed based on the combination of the surfactants and oil combinations we offer, you see that at you know the F4 and F5 SEDDS compositions are actually in micron size. However, to show it pictorially here we have, you know, shown them with a slightly larger globule size.

Now what is interesting with this SEDDS compositions is that when you look at the SEDDS compositions and you know what I was trying to explain earlier, when you look at their in vitro dissolution performance here on the left hand side, you'll see that in vitro dissolution using the standard dissolution method using apparatus 2, what you see that most of the compositions you know release almost 100% of the drug in about 8 hours and then there is no discriminatory power. There is no discrimination, you know, with this in vitro method. However, when you look at in vivo profile, you see that all the formulations you know exhibit different Cmax and AUC, which is not, which is not predicted or which is not seen with simple in vitro dissolution method. Now if you look at this, you know that means that there is no potential or there is no possibility for correlation. You know, when you look at IVIVC, typically you know I think we we expect level A correlation or level B or at least level C. But in this case here there is no possibility even for a level C correlation. It means we can't even rank the formulations in the order of potential in vivo performance.

So if you look at the literature, you know when we looked at the literature and when we looked at the currently approved products, there are multiple products which are approved. However, there is no specifically recommended method to establish the IVIVC of these SEDDS formulations. For example, you have Neoral formulation in the market where USP apparatus 2

was used with 100 mL of the dissolution media, you know at various pH to achieve the level A correlation with the AUC PK data. Similarly, you know there is a ritonavir formulation which use apparatus 2 with 900 mL of the medium and 0.7% w/v of SLS in water at 25 rpm to achieve the level A correlation. Again you know biorelevant media is recommended over simple buffers in order to simulate the GI conditions critical to the dissolution and absorption behaviors and then you know, I think one of the most significant challenge when you have lipid based system is that a sample collection process you know should include the separation of carrier droplets from the drug and I think this is very important, you know. So what kind of a filter you use? Because depending on the dynamic particle size distribution of these microemulsion droplets, you could have challenges and that's why you will see that none of the method could be replicated for any other drug candidates here. And it is really challenging and you have to develop a unique method which is suitable for your own drug product and we wanted to see if we can - if we can change this and, you know, develop a tool that could be used for predicting the in vivo behavior of this complex system irrespective of their composition.

So we wanted to evaluate this μFLUX. This is a simple method actually. If you see this is nothing but an extension of the USP apparatus 2. So you have a dissolution vessel, which is also called as a donor compartment. That is where you know you input your input, your product and then there is another chamber which is called as acceptor chamber and that the acceptor chamber, the donor is approximately around 900 mL donor compartment can anywhere from 6 mL to 12 mL of a volume and then there are two fiber optic probes, you know, one in the donor compartment and one is in the acceptor compartment. And you will see that the donor actually mimics your gastrointestinal tract, whereas the acceptor actually mimics your blood component or a blood - a blood chamber, for example. You know, and I think what - what we have here is that, you know, there is a PVDF membrane on which a lipid layer is formed. Layer is formed so that when your drug is dissolved from here and you know when it permeates through the lipid membrane into the acceptor compartment, both the drug which is permeated and the drug that is dissolved is calculated, you know, based on this fiber optic probe.

Again, before using this model, we wanted to do some literature search and you know we we wanted to ensure that you know this model works with drug products or drugs where there is pH dependent drug-drug interaction you know with different PPIs and you know that is - see here on the left hand side there was a very nice correlation which was observed with pH dependent drug-drug interactions, you know particularly with proton pump inhibitors. Either represent either with pH dependent or drug interactions with H2 antagonist or with proton pump inhibitors which is on the left hand side. You'll see that the in vitro gastrointestinal permeability correlated very well with the AUC and on the right hand side you'll see that the Cmax also correlated very well with the in vitro permeability here.

Again, we wanted to see if this model could be used for drug products, you know, to differentiate the impact of pH you know to to predict the drug-drug interactions from pH adjusting agent for example. You know if you go administer antacid with certain drugs for example, you have this phenazopyridine, you know, this is a drug which is used for urinary tract pain relief and what you see here very simplistic - what you see here is that you know when you administer this phenazopyridine and you know when you have a dissolution media of pH 1.6 or pH 4, you see that you know in blue and red you don't see much of a difference between an innovator product and a CVS pharmacy product in terms of in terms of total amount, you know which is permeated across Caco-2 media. However, when you administer, for example an antacid and when you have higher pH in the gastric media, then you know this model is able to distinguish between the innovator product and also the generic product where the dissolution is around 90% for the innovator, whereas it is only 65% for the generic drug.

So again, you know this method could - we wanted to see if it it has been used for complex drug product. It has been used for, you know, a very complex amorphous solid dispersions. And there are three examples here with the solution with the capsule, two different capsule formulations. And what we see here again, very interestingly, a you know a fasted state and a fed state data you know which is again compared with the early flux you know typically they use early flux because early flux is a better indicator of behavior in vivo. Otherwise, the later flux you know the earlier flux is typically 50 minutes to 120 minute time time frame. Because if you look at a later time frame, you know there could be precipitation of the drug and you may not be able to get very good correlation. So in this case you can clearly see that there is a positive and a negative food effect, you know which was clearly clearly seen with this method of µFLUX indicating that the method is able to distinguish between different compositions as well as different drug products, whether it is pH dependent or pH independent.

So with that in mind, we wanted to see if SEDDS formulations could be evaluated using this µFLUX method. You know again very simple as I was explaining earlier, you have SEDDS formulations, you know which are introduced into this dissolution compartment and they could exhibit into either simple SEDDS or secondary structures. Or they could, you know, exhibit there as a simple surfactant particles floating into the dissolution media, or micelles, or a free drug. And that creates a challenge for dissolution many times. And hence if you use an acceptor compartment or acceptor chamber, which is separated by a phospholipid membrane, then you could easily determine the permeation of the neat drug into the acceptor compartment. And I think this provides a very good benefit, you know that it avoids the complexities of your drug being entrapped in lipid systems, thereby eliminating the issues related to the composition, the dispersibility, the issues related to the droplet size or digestibility or secondary structures that are present in SEDDS formulations.

So this in vitro µFLUX I think you know based on this observation you can see that it resolves all of these complexities to a single parameter that could be monitored over a period of time and that is absolute drug concentration in the absorption chamber. And what you see here, you know, when we used when we used this method for the ten SEDDS compositions you see that we were we were able to distinguish or we were able to rank the formulations in the order of better potential in vivo performance, you see that formulation F2 showed us the highest permeability here, whereas the drug alone you know showed us the lowest permeability.

Now we wanted to see if this correlated well with the in vivo performance of these formulations, and this is what you see that you know in in here that all these formulations you know correlated very well. For example this F2 formulation you see very clearly it has higher flux. At the same time, it also showed higher Cmax and higher higher AUC in vivo in SD rat model and again you know, you'll see that even the drug alone or other formulations, you know, correlated very well with the in vivo data. Again, you'll see the rank order correlation here. Again, we separated the GMO based formulation and kept Capmul MCM based formulations. Again, mostly because GMO and Capmul, you know they have HLB values of around 6 versus 3 and that's why we wanted to make sure that we are able to separate when we are developing a rank order correlation. So here you see that you know in both cases we were able to get R square value or correlation of greater than 0.9 indicating that you know, this model was able to correlate in vitro data with in vivo performance very nicely, actually.

So again, this is a tool you know which could be used for potential IVIVC. And we're hoping that, you know, in future, many such models will be developed and, you know, used so that as Siva has also mention in his session that you know we could explore the potential for biowaiver at

least for fasting or fed state, you know, with this complex formulations, but you know there are also methodological constraints or challenges you know in this μFLUX based models which need further attention and further research. And I think the topmost is reproducibility, reproducibility and consistency issues, you know. Of course, we need to ensure that the membrane formation is consistent, you know, from a person to person. The method is accurate. The method is validated. There could be compatibility issues between the lipid membranes and you know, various dosage forms that need to be studied, validated and evaluated. There's complexity in analysis, specifically when we have biphasic media and how do you work on that complexity. And again there are issues related to instrument calibration constraints, you know that need to be that need to be evaluated.

But then you know with that, you know, I think this is our concluding slide. Again, we have seen that you know lipid-based compositions are complex and their complexity is you know self-evident in their manufacturing method in the components that are used and also in the in inherent challenges the way the way they behave, you know inherent challenges that could lead to that variability. However, it is certainly possible that you know with this tool which we presented today, some similar tools could be developed potentially for in future that could help us enable correlate, you know individual behavior of these formulations so that we can potentially look for some biowaiver not for at least new product development, but at least as a tool for post-approval changes with that. With this, I would really thank my colleagues at BASF, you know Nitin Ming, Roni and professor Anit Singhaler and our collaborator Pion for the excellent collaboration and the work which you see in this presentation. Thank you.

Dongmei Lu: Thank you very much Sandip, for the information about the lipid based formulation and μFLUX. And our last presentation is from Dr. Yuqing Gong and Dr. Yuqing is a senior pharmacologist in Division of Quantitative Methods and Modeling in Office of Research and Standards in OGD from FDA. And her research are focused on utilizing quantitative tools such as population PK modeling and simulation to address the specific questions related to generic drug development process and/or regulatory decision making and Yuqing's presentation title is "Enabling Patient PK Bioequivalence Studies Using MIE". Please.

Yuqing Gong (FDA): Thank you for the introduction. So today I'll be discussing the opportunities of using the model integrated evidence approaches to develop more feasible and more efficient patient bioequivalence studies. This is my disclaimer. Basically, this presentation reflects the views of myself and should not be interpreted to represent FDA's views and policies.

We have seen increasing impact of modeling and simulation in generic drug development. In 2019, we published a paper that we laid out how model integrated evidence MIE can be used in generic drug assessment and in that paper we discussed that modeling can be used to generate information not just to plan a study, but to serve as pivotal evidence to support bioequivalence and in recent years, FDA continue working on advancing research to facilitate the utility of MIE to support the demonstration of BE. And as we heard yesterday, FDA published GDUFA Science and Research Priorities report every year. So here I'm putting a snapshot from the FY25 GDUFA science and research priorities so you can see #7. It's facilitate the utility of MIE to support demonstration of BE including advancing complementary approaches using MIE to support an efficient demonstration of BE specifically for drugs with complex routes of delivery, as well as for the long acting injectable products and establishing best practices for model standardization, validation, acceptance and sharing and developing innovative study designs for PK studies in patients such as those with reduced or sparse sampling for oncology products and adaptive designs.

I think many of you may be familiar with the MIDD meeting program that where the sponsor can discuss specific modeling questions with FDA during their new drug development. So in October 2023, we FDA launched the MIE Industry meeting Pilot program where it it provides meeting opportunities for generic applicants to engage with FDA with specific modeling questions. And this can be both in pre-ANDA and ANDA stages and an applicant can discuss modeling issues for one particular drug or cross multiple products as well as complex modeling approaches for non-complex products. So wait for some of the questions that are either out of the scope or cannot be sufficiently addressed by the existing pre-ANDA and ANDA scientific meetings. So there's MIE meeting program, the aims to provide a dedicated regulatory platform for interactions on MIE. So for more details you can reference to the MIE industry meeting pilot the web page on FDA website.

Then go back to the patient bioequivalence studies. I think yesterday in session three, there is a speaker mentioned briefly mentioned there are challenges in conducting patients bioequivalent studies. So sometimes the safety consideration preclude the use of healthy subjects in PK BE studies. So in such situations, BE studies should enroll patients from whom the drug is intended to treat without a disruption patients ongoing treatment such as for antineoplastics, the anti-cancer drugs, antipsychotics, immunological agents, et cetera. So, since there are patient studies, so it was it will be associated with some challenges including like difficulty in collecting, intensive sampling in patients, high variabilities and as well as large sample size and recruiting difficulties and potential high dropout rate.

So in 2023, FDA did a survey based on FDA product specific guidance database that identified 57 PSGs for immediate release oral drugs products that recommended conducting the PK BE studies in patients. As you can see in the pie chart here. So majority of them, 70% are for antineoplastics and also there were some other therapeutic categories including the antipsychotics, anticonvulsants, immunological agents, and from those this 57 PSG 40% recommended single dose study in patient and 60% recommended multiple dose study in patients. So this survey it's only for the oral drugs, but as you can imagine there will be more. So the total number of PSGs at recommending patient studies will be more.

So the challenges always brings opportunities. So using MIE it can potentially develop more efficient and feasible patient based studies. So in my talk today, I'll be discussing some potential applications by using the modeling to design the more efficient patient bioequivalent studies. That includes some examples from like some potential applications, potential usage such as reduced or sparse sampling like alternative bioequivalence study design. For example, the crossover study without washout. And I will also discuss MIE BE framework that was developed by our collaborators as part of the GDUFA funded research and some compact design like adaptive design so at FDA we see a clear demand increased use of modeling approaches in Pre-ANDA interactions and ANDA submissions.

So here I'm putting the first potential application that use MIE to support sparse PK sampling design. As you may know for some patient study collecting, rich sampling like 12 to 18 samples may be difficult. So here I'm putting an example PK profile and an example design where the sparsely sampled populations can be collected by groups to help characterize the full PK profile. So instead of collecting 12 or 18 samples per person, it groups to different groups that collect 5 samples per person. So by leveraging population PK modeling that allows pooling data from sparsely sample populations. So it can help to characterize the full PK profile and test to reference ratio. As the PK modeling can recognize sources of variabilities and incorporate covariates to better characterize and compare the drug exposure from sparse data sets. Of course, for this type of design, the very important part is to design the optimal sampling points

that can help this sparse sampling design, for example like you will need an optimal design that can capture the absorption well, like maybe more sampling around the Tmax, but reduce sampling for other time points.

The second example here I'm showing for the potential opportunity is to use MIE to support alternative crossover design. Here meaning the crossover design where that you cannot do washout in patients. So in some cases steady state crossover study in patients cannot be achieved either due to irregular dosing frequency or the length of the treatment. And of course single dose crossover cannot be done in many cases in patients because cannot perform the washout. So as I show in the figure here, so using modeling can potentially provide feasible crossover design on in this case where we use modeling to adjust carry over in the crossover study when the washout is not feasible, which means removing the drug carry over via the population PK modeling. So using this design, it allows crossover power equivalence comparison. So when compared with parallel study, so it provide, it can get smaller sample size in the study.

And here I'm showing the MIE BE framework that was developed by Uppsala University research team, doctors Andy Hooker and Mats Karlsson. So this was part of the GDUFA funded research. So here I'm showing the MIE BE framework that Dr. Hooker presented in the FDA CRCG workshop. So this MIE BE framework includes 4 steps. Model building, uncertainty estimation, simulation and conclusion. So basically it take the bioequivalence data and models for model fitting and during the model fitting it's important to identify the treatment effects mainly on absorption parameters and then in this framework it estimate model and parameter uncertainties using the uncertainty methods such as SIR, the sampling importance resampling, bootstrap model averaging and then from those candidate models it simulates a number of simulations like 500 or thousands. Then from all the simulations it compute individual Cmax AUC. Then you'll get the mean ratio of the Cmax AUC for the T/R ratio and a distribution of the mean ratio from this a number of simulated trials and then eventually can calculate the 90% confidence interval from this distribution to get the BE conclusion from these simulated trials.

By collaborating with university, we have completed several FDA contracts that showed the potential applications of this developed MIE framework that includes the BE evaluation for highly variable drugs with an incomplete washout design and BE evaluation with sparse data and BE evaluation at non-steady state PK. In this case, the contract studied the switch design where you no longer wait until steady state for period 2, but you measure the first dosing interval right after switch, so that saves the time for conducting the steady state design. So you can reference to those papers that are listed here for more details of those research.

So by the successful development of ICH M13A ICH now start beginning to develop ICH M13C. So we in M13C we know they would be discussing more complex designs such as adaptive design. So adaptive design is a clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on the accumulating data from subjects in the trial, so it provides some opportunities of stopping a study earlier or adjusting the sample size during the conduct of the study and adaptive design also can can be grouped sequential design or some other design with one or more adaptive features. Here I'm putting one FDA research that went from Dr. France Mentré's group that is, study the model based approach for group sequential and adaptive design that coupling modeling and adaptive design together, and you can also reference to this presentation that is available online for the details.

I think I showed several potential applications using modeling to help design more efficient bioequivalence studies. Here I'm putting some regulatory considerations where we always ask

ourselves and applicants when we see such MIE design. So the 1st and the most important question is how the MIE approach meet can meet the regulatory standards to generate bioequivalence evidence. How to ensure the unbiased equivalence determination for the formulation difference assessment and how to characterize the uncertainty and propose an appropriate bioequivalence statistical method? And of course, since this is a modeling approach, so the sufficient verification and validation is important, how would be the appropriate model validation strategy? For example, some additional model validation strategy may be needed using more quantitative measures beyond the general predictive diagnostic checks and how much prior data are needed to propose and validate an MIE approach. And the model development and validation process and criteria should be pre-specified as using MIE approach in BE assessment should not be interpreted as post hoc analysis that may lead bias to BE reduced and FDA is also continually working on to develop the best practices of MIE approach in regulatory submission and standardization of model sharing, submission and communication. I also put a link here for the docket to the model master file.

So I like to acknowledge my management and colleagues at ORS Dr. Andrew Babiskin, Dr. Lucy Fang, Dr. Karin Lee, Dr. Rob Lionberger and Dr. Lei Zhang. And in the end, I look forward to hear some comments during the panel and seeking the inputs on future research under the GDUFA research and Science program. Thank you.

Dongmei Lu: Thank you very much Yuqing. And so we're going to have a break and audience and the break is until 11:00. So please come back on time. And for the audience? Oh, sorry for the panelists from industry and also FDA panelists. So please come back around 10:55. OK. Thanks.

Panel Discussion

Moderator: Pleasure to moderate this discussion here. The goal for us in the panel session is really to hear from the industry what research the FDA needs to prioritize to drive the efficiency of the bioequivalence approaches for IR products with complex formulations. As Dongmei mentioned earlier, we also welcome comments from the virtual and in-person attendees and please consider those comments, like for the FDA, those comments which we are submitting either to the docket or if you're coming up to the mic, those are equally important and we kind of consider them or give them similar weightage.

So for this panel session, the format we're going to do it a little differently from what we did yesterday. We have an excellent panel of experts from the FDA lined up over here, and each of them has expertise in many areas, but based on the nature of their day-to-day work, they will have expertise more like they'll be more interested in asking questions in their area. So what we want to be doing is yes, I will start with some of the early first few one or two questions but then our panelists will also kind of chime in with their questions and we'll have a free flow for the panel discussion. Let's make it as interactive as possible.

So with that first I'll introduce the additional members of the panel. So here from the industry, in addition to the speakers we have Dr. Emilija Fredro-Kumbaradzi, who serves as the director of Biopharmaceutics and Statistics at Apotex. And then we have Dr. Russell Rackley. Russ is the global head of clinical pharmacology at Viatris and Russ is also a member of the ICH Expert Working Group. So we have some ICH people represented here.

And then from the FDA, I'll just introduce our panel here. To my left we have Dr. Hazem Ali. He's a review chemist in the Office of Product Quality Assessment One, Office of Pharmaceutical Quality. Then next we have Dr. Bhagwant Rege. He is the division director for Biopharmaceutics in the Office of Product Quality Assessment One, Office of Pharmaceutical Quality. Then we have Dr. Diana Vivian. Dr. Vivian is the associate director in the Division of Bioequivalence Two, Office of Bioequivalence, OGD. Next we have Dr. Fang Wu. Fang is a senior pharmacologist, reviewer and scientific lead for oral PBPK modeling in the Division of Quantitative Methods and Modeling in the Office of Research and Standards, OGD. Dr. Lei Zhang, she is the deputy director of the Office of Research and Standards in OGD, and Dr. Qi Zhang. She is the lead pharmacologist in the immediate office in the immediate release drug product team in the Division of Therapeutic Performance Two, Office of Research and Standards, OGD.

So with that we can get started with our panel discussion. We heard some very great, very informative, interesting comments from all our speakers and thank you so much for that. Our speakers, they touched primarily on the challenges with the complex formulations, the ASDs and the LBFs, the lipid based formulations for the IRs and as we heard earlier, M13 recommends fasted and fed studies for both. But M13A also supports alternate BE approaches. And what we heard from the presentations is that clearly there is a desire to reduce the number of studies by pursuing this alternate approach, whether it's modeling and for that like PBBM, PBPK, IVIVC, those were mentioned or it could be the in vitro characterization but both the industry and the FDA recognize that predicting the drug and food formulation interaction for complex formulations, that remains a challenge. So that's the bigger elephant for us to kind of counter.

So with that, the first question that I have is like given that the mechanism of the food formulation interaction is not well understood, if a fed model is developed using the innovator data or the literature data, what additional understanding or research should we do? We need really, so the model will work for a generic product which has a different formulation and for us like we only kind of limiting ourselves today to the ASDs and the lipids. So I'll pose this question is not particularly to anyone we would like to hear each of you are experts also over here and we would like for each of you to comment and give us some input give your thoughts so that like how do we translate all that was kind of presented into research? So anybody want to start first or?

Sandip Tiwari (BASF) Thank you. Thank you, Nilufer. Maybe I could break the ice here. Again, you know, I think if we look at these complex formulations, currently we are at a stage you know, particularly if you look at the lipid based formulations, you know even level C correlation seems to be challenging and there are inherent differences. There are inherent differences between the product and innovator that is linked to the complexity of the lipid based formulation themselves. But looking at the promising data we have seen and also you know we have seen in literature with other models, it seems like at least we are heading in a direction where potentially you know the rank order correlation certainly is going to be feasible. You know, with these methods in the near short term, you know, of course we need research in terms of validating those models, ensuring that you know they are reproducible.

For example, you know the model which we talked about on microflux based systems, you know which combines dissolution as well as permeability. The challenges, as we explained in the presentation is that we also need to have positive and a negative control developed in a similar to the tablets we have, you know, for example, for dissolution studies, you know for mechanical calibration and validation. So I think definitely more research is required. You know on the type of the lipid systems that could be used as membrane. Type of candidates that could be suitable

for positive and negative control, for example, and hopefully you know that kind of research will pave the way for developing the systems that will help us not only in rank order, but also predicting some fasting and fed effect, you know because in literature, what we have seen is that particularly with lipid based systems, even the fasting state study could give you an insight on potential fed state behavior. Because of the lipid nature of these formulations, again that will depend on how much of dosage is administered and you know what kind of a composition it is. But certainly preliminary indications are that that kind of you know discrimination is possible to be predicted. You know with this at least complex lipid based systems.

Moderator: OK. Thank you. Thank you. Yes, go ahead.

Girish Nihalani (Hikma) I mean very difficult answer. There will be will not be one approach which which will fit correct all molecules. But I was just thinking what could be the practical feasibility and acceptance by FDA. So some scenarios which I can think of like during development we do multiple pilot studies so say a product failed in the fasting study, but passed in the fed study at a 3% weight gain. And then the formulation was improved to pass the fasting study the percentage of coating weight can say increase to 7%. And it made the fed criteria. So in both the instances 3% or 7% made the fed criteria. So any future formulations, say containing 5% weight gain is obviously expected to meet the fed bioequivalence study criteria because the three and seven percent are meeting, so in those cases the FDA can consider to waive the fed study if 3-4-5 percent weight gain. Those kinds of things. And when we talk like a variable food effect from which our composition base. So here the models will be highly composition specific with regards to the SEDDS. If I ask specifiers is used in the systems and some consideration could be if they are qualitatively similar to RLD and in some of the instances innovator does submit the in vitro and in vivo relatable models to FDA. I'm not sure if that'll be shared by FDA to facilitate the generic drug developers rather than investing time and energy in discovering and discovering the model, one which will fit then the one submitted to FDA, assuming the qualitative compositions are similar.

Moderator: So like when you are developing your products, you would also have an understanding of what are the critical aspects, the critical attributes of your formulation, right. And so when we see some generic versus the test and it differs only in a little bit of surfactant or let's say if it's an ASD and the two polymers are different. But they the release mechanism because they are both let's say they're both hydrophilic and the release mechanism of the both will be the same. How critical is this? Like you know, yes, in in vitro you saw something, right? But how does that translate in vivo? And if we don't know, how do we translate this information or the knowledge to a research project? Because here we are only we're trying to get like you know what type of research do we need to pursue. You, you, you are like developing a lot of products and you have a good understanding of that. And so that's what we are we are wanting to kind of understand what is that? What are those critical aspects and what? What do we know versus like? Where do we go from here? So I'm just wondering if you are able to share from those experiences with us?

Sandip So in terms of the two polymers having the same release mechanism, but still there could be potentially in vivo differences in performance, so the in vitro tools we look at how sensitive those two polymers are with respect to the different in vitro dissolution condition of the respective molar concentration buffer concentration. Many other medias, we see releasing incomplete drug release, but it still be extended beyond two hours, 3 hours even for IR dosage form just to detect those differences.
So ultimately goal is to find some tool here in vitro which can correlate the in vivo performances to the and in vitro observations. And the release mechanism.

Sivacharan Kollipara: Few details, sorry, sorry for interrupting please.

Moderator: Let me go to Emilija Fredro-Kumbaradzi. And after that, if you don't mind.

Emilija Fredro-Kumbaradzi (Apotex): This is a very interesting topic. Generic industry starts always with a deep dive into the innovator's product. So we need a very thorough understanding. We go through deep literature search, we do a lot of different in vitro test in order to characterize and understand the innovator. Based on the formulation strategies, sometimes we are following the same polymer sometimes maybe mechanism is the same but polymer is different. And in that case, we do always a battery of comparative tests between the innovator and the generic product. And that being said, we identify the differences. If we find the condition that we believe is more relevant to fed study, we assess how our formulation compared to the brand. So all is comparative and then we have a literature data say brand has a positive or negative food effect. It's already reported our in vitro tests are interpreted in that manner. Accordingly, we get an understanding and some of others are saying how our formulation and how changes in our formulation parameters are reflected on those in vitro performances.

In terms of modeling of fed study, there was a good point brought how much we can use the literature data, how much we can use virtual assessment. If it comes to conducting an in vivo study to verify or validate the model, then we will do fed study pivotal rather than pilot and do modeling. So it's all about of balance. How much work? Generic industry? Should do to justify with scientific work. And in certain cases, justify scientifically sound that we can waive a study. So we definitely know that more work is required about in vitro techniques. New techniques or standardization of the existing one, because execution can also vary. So being scientist of both sides, industry and FDA, we come up with scientifically sound and standardized in vitro technologies that we can use to see if, if we can properly assess the risk and justify biowaiver of the fed study.

Moderator: Yeah. No, thank you, Emilija. So if I can follow up a little more. Like you mentioned, in vitro techniques, right? Yeah. So in vitro characterization would be very helpful. Can you share some thoughts on what what type of in vitro techniques you use? Have in mind like your or what type of research is still kind of needed to advance these in vitro techniques.

Emilija Fredro-Kumbaradzi: Yes. So. First we need to have more of a dynamic dissolution techniques. When we simulate changes that happen in our gastrointestinal tract. Conditions to be optimized to be as close as possible to in vivo. We know that there is always a difference between I don't know, dissolution of vessel and gastrointestinal system. But using dynamic changes and simulating the events in the gastrointestinal tract that may be relevant to the form. That is what we are looking for. We know that lipolysis when it comes now to fed study prediction like lipolysis is something that is not simulated in any type of dissolution system. And can play a significant role and can be very complex. Depends on what polymers are being used, how the polymers are being digested, how that impacts precipitation or solubilization in vivo. So these are all the opportunities for research for different types of systems which are enabled approaches. how? What are the parameters to be studied for each of these type of systems? Which would be most relevant to predict in vivo performance?

Moderator: Thank you. Siva, you wanted to share your thoughts?

Sivacharan Kollipara: Yeah. Thank you.

I think the I I hear some echo.

Moderator. We hear you fine.

Sivacharan Kollipara: OK. So in conjunction with what the previous speakers have mentioned it is important to understand the reference product behavior. What is the polymer which has been used? What is the surfactant? What is the surfactant level and then initially we can characterize the test product against the reference product using variety of test especially in case of solid dispersions. We have observed that rather than the thermodynamic solubility, the kinetic solubility can give significant understanding. For example, if you have a solubility test performed at one hour, 2 hours and 4 hours, then we have observed that the solubility at the specific time point correlating with the Tmax has given some good amount of understanding in some cases. The dissolution also has worked depending on the polymer amount, the dissolution test can become a little more sensitive.

The situation gets little complex when we have pH dependent polymers or hypromellose acetate succinate. In those cases, the dissolution testing at the polymer break even point, for example, some of these polymers are also enteric coated polymers, so that dissolution behavior at pH 5.5 or pH 4.5 to 6.5 can give critical information about the test product performance against the reference product.

Then coming to the modeling related to the food effect, it is important to understand the type of mechanism of food effect that is being observed. Say for example if the reference product has a positive food effect, then obviously the resulting mechanism is due to the solubility or dissolution enhancement, and that particular mechanism can be incorporated in the model. And if you are able to account for the positive food effect of the reference formulation, similar battery of test can be done for test formulation and then we can be able to simulate it. But if the reference formulation is exhibiting a negative food effect, there could be multiple reasons - reduced disintegration time, reduced dissolution, pH dependent solubility, transporter's effect, or the chelation with bile salts, or the multivalent cations. So it is important to understand the reason for the negative food effect and then accordingly incorporate the mechanism in the model. Then you do the battery of similar test for the test product and then get the in vitro characterization and then we can incorporate into the model and then understand what is the type of food effect that we are getting for the test product.

And ultimately, with the appropriately identified in vitro test combined with the model, we'll be able to predict the bioequivalence under the fed condition for the reference as well as test products. So the situation is that it all depends on the type of formulation and the type of polymer which has been used in the test and reference product appropriately. We need to come up with the in vitro tests followed by the modeling and simulation approach.

Moderator: Thank you.

Charles DiLiberti (Montclair Bioequivalence Services): Hi, Charles DiLiberti, Montclair Bioequivalence Services. Let's face it, the fed state is extraordinarily complex, and I think because of that we should consider an intermediate approach instead of requiring either a full pivotal bioequivalence study with 80 to 125 confidence intervals or no fed bioequivalence study at all. Maybe we should consider an intermediate approach where you require a small fed study. Either with no criteria just to collect information, because I think we need to build up information on the relationship between in vitro and in vivo, and one way to do it is to require small study or you have relaxed bioequivalence limits like the old bioequivalence limits for fed state, which was

70 to 143, but I think an intermediate approach where you get some bioequivalence data just to make sure there isn't something really bad going on. Maybe that makes some sense? I'd also like to point out that maybe for the big companies, the big generic companies where they can do their in silico modeling in-house, it's not so onerous to do modeling because they do it anyway. But for the smaller generic companies that have to outsource modeling it can cost more than a bioequivalence study. Thank you.

Moderator: So. Geoff, did you have to wanted to add anything or can we move to the can move to the next question?

Geoff Zhang: Well, I know everybody wants to do less clinical trials and save money, but I do want to caution everybody that just from whatever data we know so far from the drug goes into the GI tract to all the way the drug in blood, there's so many steps in between in order for the drug to get really well solved. None of those that can screw up. So and then we also see that tiny bit change of things. We have a big impact assuming the droplet rates are really critical, which is a big question as as of now, OK, if it turns out that, yeah, the droplet rate is really critical and the size of those are really critical, a slight change of surfactant vendor. And I've seen even lot to lot from the same vendor. Can lead to the differences of those droplets size. So so I just want to caution everybody that yes, we have good thinking. We want to save that. But the reality may not be so that we can save those things, and I think we need more mechanistic study to really understand every step elementary step so that we know, OK, first of all. Is it critical second of all? Small amount of excipients in your formulation. How does that impact on the critical attributes that that you have so? Just want to caution everybody.

Robert Lionberger: All right, I have a question for generic industry panelists. How often would you use one of these novel technologies that we talked about today like solid dispersion, self-emulsifying system when the brand product that you're trying to mimic didn't use those, how how in the space, how much is that in the space? Because our M13A updates basically, you know, sort of assumed that they're an analysis of the risks of the brand product. Saying the brand product is a conventional formulation, if you also make a conventional formulation you don't have to do fed studies, so how often? Do what a generic the generic industry consider using one of these novel technologies when it's not present in the brand product? And the second follow up, that is like how much constraints that I know one of the proposals was to look at, I want to make my product Q1Q2 the same as the brand product and then do less studies like how feasible is that for these advanced technologies in terms of intellectual property protection and understanding the excipients at that level. So I think those two questions like how much are those two activities in the space of what the generic companies are considering when they're doing formulation development.

Russell Rackley: Yeah, just to comment on the first point. I don't think it'd be very likely to pursue a more complex formulation when your reference target is, you know, maybe more conventional. I think more you know, not being a formulator I would you know, not venture down that road. Ideally, the preference would be stay kind of more like the brand or the reference in terms of development and conventional? As far as the second part of the question, I have to defer some of the more formulator experienced folks, but I would say that some of the comments already from Emilija, and I think Charlie mentioned as a sponsor, we have to gauge what is the return on investment pursuing you know a kind of model based approach for virtual bioequivalence something like that as opposed to, you know, getting to using the science now, there's a lot of good science here that's been presented. And I think this is advantageous overall to you know, propelling, you know, development of drugs, be it brand and or generics, but you know, to what extent do we tap into that? And make that judgment call as to whether to go very

far to the point of, you know, validating. You know, an approach to satisfy an agency versus using those tools to develop a product that gets you to the point you say, OK. I'm good enough to go and just do the bioequivalence study. That's kind of the trade off. So just thought I'd throw that in.

Moderator: Charlie, a quick comment because we want to move to the

Charles DiLiberti very quickly follow up to Rob's comment. I think the question to broaden it is how often might an innovator product use one solubilization enhancement technology and because of the patent you're forced to use a different solubilization technology. So they both might be complex but different technologies.

Moderator: Yeah. Yeah, we understand those challenges, right? You know, would you want to like from the ICH perspective with you know, we have been doing grants and research already on in this area? Anything that you would want to add?

Fang Wu: Yeah, yeah, I think I appreciate our industry colleagues share your thoughts and examples. I think we FDA supported the research also being conducted in this area. I think you cited in some of your slides. Because the ICH M13A indicated that the modeling can be used for supporting the rationale of waiving BE study fasting or fed and actually the ASD is one of the high risk products. We support those research and then if you have seen and we have published at least three publications based on the FDA support GDUFA supported research. One of those is for HCTZ, ASD. Some of the formulations they have positive food effect. We are developing the biopredictive dissolution and put it into the model and then can capture the in vivo food effect for positive and also some of the negative food effect for different formulation also. But that's depending on the formulation itself. If it contains the pH independent, maybe it has positive food effect that could be incorporated into dissolution with the add the bile salt and add some surfactant and mimicking the food condition. That's one of the considerations when we develop modeling for predicting that positive food effect.

But it's a little bit challenging for the negative food effect as mentioned by Siva and for those type of the formulation with negative food effect with ASD, we know that there is one actually have the pH dependent polymers in there and then you can see that in that application that the biopredictive dissolution can be used like a three stage the fasted fed and with different pH and mimicking that situation and in that case that productive for the company indicated that you can look into the literature publication for for that we that's for the BCS class two drug. Of course, we also have some other GDUFA support research for BCS class 1 and 3, how that sometimes the negative food effect can be observed for those type of the drug and what type of the dissolution or biopredictive dissolution or in vitro testing can be used for incorporating into the model and predict those. Those are the research we have conducted, but those are a few examples.

So now I think we also can think about the gaps, even though we have conducted some research, understanding more of the of these and how to use the model and predictive. But I would like to emphasize actually we need to understand more and more cases, especially the release mechanism, because the different formulation can sometimes have different, especially when you compare generic and RLD, they may have the same release mechanism then the modeling could be kind of. You can use a similar modeling, but if they don't have the same release mechanism, you may need to adjust the modeling and also consider what is the best biopredictive dissolution that can be supported by the modeling, so modeling can help for identified biopredictive dissolution also can support the virtual BE simulation. If you have the model validated using the data that is available so that is like point is that understand the

release mechanism and understand the food and the formulation interaction. For your formulation your generic and RLD whether they are similar or not and incorporate those into your modeling and use modeling. That's what modeling is one like evidence and but if you have other evidence like that, maybe a formulation comparison and also dissolution comparison in multimedia and also biorelevant media biopredictive dissolution method or other in vitro testing method, then yeah you can use all of those the total of the evidence for supporting the justification of your waiving BE study fasting or fed. Thank you. Thank you.

Moderator: Yeah. OK. So maybe we can move to the next topic which we wanted to talk about and that's related to…

Lei Zhang: Yeah. I just want to make a quick comment by listening to today's discussion also reflect how far we get to today, because this is really our recent M13A to recommend one study for non-high risk is really accumulative research in the past 10 years as Rob mentioned yesterday. We did revise more than 800 PSGs. This also reflect just look at the landscape. 72% of the current approved drug are considered non high risk. So we only need one study. That's the majority, but we still have 28% still recommend two studies or they already been existing. One study I think only like half of them like 14% of them are high risk product. This based on the formulation this is probably what's our focus today? But we also have another 14% either there are narrow therapeutic index drug or drugs to be recommend to be studied in patient probably already we only recommend one study but they have other challenges. Like what Yuqing mentioned in her presentation, as well as some drug, we already recommend one study. So I think we should we should be very pleased, at least we probably today is more focused on those small subset and also we heard today's presentation. There's still very heterogeneous among those formulation different strategies.

So I welcome the audience both online in, in the room to submit your additional comments, feedback, email. We did not discuss today to the docket. So FDA can take consideration because those signs not only help the industry for the external research, but also internally when we review the PSG, when we doing the M13A implementation, we also have a lot of questions on how we assess risk a particular drug and what we can recommend in the PSG. There's still some area we feel like is not as clear as we wish it is, but we want to be able to based on the research, to make our guidance more clear, give you very clear recommendation for the for the drug development. So I just want to put this on the table. I know there probably will be more discussion. It's very general comment. Just only not only the ASD but some other area you think will help for the M13A implementation as well as the IR product in general, I think if we don't have time to discuss here live or you can always submit your comments to the docket. Thanks.

Moderator: Thank you, Lei. And maybe now we can move to the other part that we wanted to talk about is like the in vitro characterizations and hand it to Bhagwant to ask the questions, right.

Bhagwant Rege: So we've been discussing how to get some of these high risk products and how to make them a pass BE with just one study so. I've heard about Q1 and Q2. Q1 and Q2 for oral immediate release product could be constraining to developers, but can we have category where similar to what we have for semisolids we have no different standard. So could we? Could we develop some of those similar standards for each of these different technologies and then have in vitro characterization based approaches? Especially if they're very close to Q1 and Q2 a set of tests for each of these technologies. Again, we maybe we need additional research in, in those and based on that we could potentially waive one of the studies and as you

move away from Q1Q2 like properties, then you will need additional evidence including modeling, modeling and simulation type of evidence. So that those are some of my thoughts so. The closer you are to the innovator product composition and not just composition, we're also have to think about manufacturing process because even if you have same composition, spray drying and hot melt extrusion are very different processes. So do they behave the same even though your composition might be the same? So that's another thing that we think about.

Moderator: So Bhagwant then maybe the question to our panelists would be like, you know, what are those two to understand those elements of the formulation? How how critical is it that the surfactant should be similar? Or the plasticizers like, you know Jeff, you mentioned plasticizers. The polymer that the and the type of the polymer and how to affect the release and you also mentioned, yeah, surfactant, plasticizers. At least those three I got from your presentation. So like what are how critical is this? Like you know, yes, in in vitro you saw something, right? But how does that translate in vivo? And if we don't know, how do we translate this information or the knowledge to a research project? Because here we are only we're trying to get like, you know what type of research do we need to pursue.

Geoff Zhang: Yeah, that's a big question. But funny, you mentioned that manufacturing process, I think you guys had a collaboration with Lynn Taylor on the generics of tacrolimus. And. So fortunately that ASD when you look at the dissolution, you see the differences. OK. And you also have clinical trials to show the exposure difference? The Cmax is different and is correlating to the dissolution rate? You see in vitro. So see, you guys are very fortunate to to have the right model compound and also have a different options of of the the generic products look widely so if you look at the the generics that that's used in those in that in their study, most of them they look the same as the innovators. The dissolution rate profile looks the same. And although you haven't done it in clinical trials but during the approval they they have clinical trials. So. So I say it's still hard for me to pin down one thing, but I'm just being very cautious. The sameness for the ASD product.

So if it's a immediate release crystalline drug, all you need to do is disperse the API particle and get wet, and then you have a lot of knowledge on the rate of dissolution from the crystalline material. But when it when it comes to ASD type, there are a lot of things happening in the process of dissolution. So for crystalline it's very, I want to say clear cut mostly. It is diffusion from the surface of the solid into the bulk of the solution, however. In the solid dispersion, the situation is much, much more complex. There are a lot of things happening in that little interface, so we spend a lot of time trying to look into what's happening in that little gel layer on the surface of the ASD and what's the consequence of all those observation that we have droplets or not. There are a lot of things happening right there. I would say in the time scale that's relevant for absorption. So I really cannot give you one thing that. Put it this way, I cannot define a research project as of now. I really have to spend a lot of time thinking about and trying things to define a research project.

Moderator: you have until July 7th. What July 7th? 17th. To go to submit something to the docket. All right.

Sandip Tiwari: Yeah. In addition to the point, you know, Bhagwant, you mentioned about the manufacturing process. There could also be the impact of, you know, particle size distribution of some of the polymeric materials. You know, in terms of how it enables the manufacturing process, you know, not necessarily the impact, but then that ultimately results in, you know, subtle differences in the performance. Also the source of some of the polymer excipients you know can have profound impact. Not necessarily on the performance, including performance,

but also on some of the impurities, you know which we see for example nitrosamine formation. There could be significant impact. So those subtle differences should be considered for not only their in vitro dissolution performance, but also you know other critical quality attributes.

Diana Vivian: Thanks. So I'm also in that similar line I'm interested in if you think more research is needed in the post approval space. If there are formulation or manufacturing changes or even pre approval if there are test product changes. Right now we have the SUPAC guidance which we generally use to determine whether an in vivo bioequivalence study is needed and that is 30 years old. So there may be some updates that could be done to that and then with this new concept of high risk drugs in ICH M13 it says that generally for any formulation or manufacturing process changes, the same principles should be applied for whether you know if an in vivo bioequivalence study is needed, whether we need both fasting and fed studies, unless there is some other justification or support, and generally it could be lower risk then coming in with a brand new product depending on the actual changes that are proposed. So I wanted to hear your thinking on whether research is needed in that area.

Sandip Tiwari: I think that is certainly a great comment. You know, I think you made about potential differences in the guidance document. You know, in light of some of the things that are upcoming in a particularly do you know with impurities and other stuff you know that might need to be amended over period of time eventually because that is a critical quality attribute for a product. So I think that is certainly a good news and I think as an industry we're looking for those guidance documents to be made available as soon as possible.

?: Just to follow up on Dan, I think that I think points to probably the need to have more or newer in vitro methods that can predict in vivo performance, so perhaps that's an additional need there.

Diana Vivian: Yeah, I think that something like that could definitely be helpful towards bridging formulations of manufacturing process differences without in vivo studies. You guys have any other thoughts?

?: Yeah, but I think there is also one complication here is that you know, how do you link, for example, in a dissolution performance to something like a totally different attribute which is related to impurities for example. There could be challenges or burden on manufacturers, you know, to try to find and develop suitable methods.

Diana Vivian: Right, I think.

Bhagwant Rege: I think we're here mainly focused on bioequivalence, so impurities that's of course it's an important topic, but it's a little different. But again, dissolution need not be the only tool writing the toolbox. That's just one of the tools. You could have other characterization for for like you're looking at globule size distribution. You're looking at composition of lipids. In terms of ASDs, again the nanoparticle characterization could be additional to. Again, none of these are standardized right now, right? These are all research tools. So can there be additional development if those in in terms of in vitro characterization?

Moderator: So we are past our time. Lei if you, Yeah, if you want to make a last minute comment and then that would be the last thing.

Lei Zhang: Just I think we didn't talk about modeling. I just have one question also for the panel regarding we I think bring up the some other model like a physiology model. I feel like this is a

good opportunity for model master file, because I think Charlie also mentioned about some big pharma or some company may have the resource to develop those in silico models. So I just wanna you to comment on what's the challenge when you use the modeling in your generic drug development. What do you think? Additional research? Additional help? Like as a community we can supply because ultimately we want to bring efficiency to the drug development enable more biowaivers if we could, by using the model by using virtual method in silico method. We just want to see what could be the barrier current exists and how we can remove that barrier. That's a question for for for everyone pretty much just see. I hope you're aware of the model master file mechanism which also have a workshop last May and a paper on the opportunity for oral product was just published in Pharmaceutical Research. So I want to bring that attention to see whether you can have some comments, thoughts on how we bring additional research in that area. Thanks.

Girish Nihalani: I'd like to just quick comment on the SUPAC thing which you mentioned. So it'll be better if the SUPAC can identify how the excipients are classified with respect to complex system ASDs credited versus a convention, for example, a binder which might be used at very low concentration in the Convention forms, for example, copovidone is used at a very high level in the ASDs, and also in context to avoiding the multiple clinical studies right now, the SUPAC 2 limit has a very low limits very for very common nonfunctional excipients like next year it cross power runs. Those may be in agency, can think of widening those limits if justified by the rapid decision disintegration. So that the clinical study can be avoided.

Moderator: All right, so thank you.

Sivacharan Kollipara: Yeah. Am I audible?

Moderator: So we are past our time, if you don't mind, dear. I'm sorry.

Sivacharan Kollipara: OK, sure. Sure, sure, sure.

Moderator: Yeah. So a very interesting, very good conversation and interactions that we had, but like, unfortunately we'll have to end panel discussion here. But feel free to have side conversations like you know, these are important points that everyone is making. Thank you. Thank you all very much for your time and thank you to all the speakers for like you know, making your contributions and coming here all the way to kind of talk to the FDA. Thank you so much. Thank you. So the lunch break until 1:00 PM and please for the panelists. And please come, panelist. So for the MR please come back as a 12:55. Thank you.