FY 2026 GDUFA Public Workshop – Day 2: Edited Transcript

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Introduction to Day 2 and Session 3

Ahmed Zidan, PhD *(Sr. Research Pharmacologist, DPQR V/OPQR/OPQ/CDER/FDA)*

Good morning and welcome back to the day two of the GDUFA public workshop. And thank you for joining us for what promises to be another engaging day of the scientific discussion and collaboration. Yesterday, we explored 2 important areas shaping the future of genetic drug development and assessment. Session one, and it was focusing on nitrosamine impurities. And session two, focused on the practical application of AI and machine learning to support the genetic drug development. So building on these discussions, today program turns our attention to three important areas that are central to the future of evolution of genetic drug regulations.

We will begin with session three, which explores opportunities to expand regulatory flexibilities through science-based bioequivalence standards, including predictive tools, mechanistic understanding, in vitro characterization, PPBK modelling, and approaches that may support the broader global harmonization.

So together, today's sessions will be a very cooperative and engaging sessions. And with that, I'm pleased to begin session three, and I will leave it to our moderator, Dr. Andrew Babiskin and Dr. Yan Wang.

Session 3: Expanding Regulatory Flexibility with Bioequivalence Standards

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Co-Moderators:

Andrew Babiskin, PhD
(Deputy Division Director, DQMM/ORS/OGD/CDER/FDA)

Yan Wang, PhD
(Deputy Division Director, DTP I/ORS/OGD/CDER/FDA)

Andrew Babiskin, PhD: Good morning, everyone. This is session 3 for expanding regulatory flexibility with bioequivalence standards. This session will run a little bit differently if you attended yesterday. We will only have one presentation, but then followed by approximately one hour discussion. This session works for research opportunities to enable more flexible science-based bioequivalence approaches. Discussion will focus on moving beyond current criteria such as the Q1-Q2 sameness toward mechanistic understanding, expanding biowaware space and biopharmaceutical classification system classification, strengthening in vitro and vivo linkages through a robust in vitro characterization of formulation and manufacturing effects. And leveraging predictive tools such as PBK modeling, identifying opportunities to support global harmonization of BE standards. Now you can tell by the summary that is a very broad session covering a wide range of products. So I just ask that as we move through the panel, the panelists here that we are descriptive of what type of products we're talking about, but we can also talk in a more broad sense.

Our first presentation, and our only presentation within this session, is from Abhishek Gupta, PhD from the Chief Scientific Officer at Transpire Bio. His presentation is the recent development and experience of the utilization of non-standard in vitro characterization tools to demonstrate bioequivalence between Reference and test drug-device combination products. At Transpire, Dr. Gupta is responsible for the scientific direction of Transpire Bio. As a member of the leadership team, Dr. Gupta is responsible for providing the strategic and operational leadership to develop and implement the company's scientific strategy, overall product portfolio, and conceptualization and introduction of new product opportunities. With that, I'll turn it over to the presentation. Hopefully, Doctor Gupta's online.

Presentation 1: Recent Developments and Experiences with Utilization of Non-Standard In-Vitro Characterization Tools to Demonstrate Bioequivalence between Reference and Test Drug Device Combination Products

Abhishek Gupta, PhD *(Chief Scientific Officer, Transpire Bio)*

Abhishek Gupta, PhD: Yes, Dr. Babiskin, thank you for that introduction and a pleasure to be here. Hopefully you can hear me okay.

Andrew Babiskin, PhD: Yes, we can hear you.

Abhishek Gupta, PhD: Great. Are you able to see my slides?

Andrew Babiskin, PhD: Not yet. OK, there we go.

Abhishek Gupta, PhD: Excellent. Thank you. Morning, everyone. Pleasure to be here. Thank you, Dr. Babiskin, for the introduction. Also, thank you, Dr. Yan and OGD for the invitation. Again, I am very appreciative of the initiative that the agency has and the OGD in organizing this workshop. So the conversation today is going to be focusing on drug device combination products at a high level on the combination products. And I intend to cover some recent experiences there in terms of in vitro vectorization tools to demonstrate the bioequivalence of the BE between test and reference products.

So before we go forward, a quick disclaimer here. Any views and opinions that I express here are purely mine and do not represent those of Transpire Bio. So with that, let's take a quick look at a very high level, the legal definition of combination products. These include drug device, biologic device, drug biologic, and drug device and biologics. So if you look at these, these can be physically, chemically, or otherwise combined or mixed and produced to form a single entity. And so that's a broad definition. For the purposes of today's talk that I'm giving here, I'll ignore biologics for the most part and focus mostly on small molecules and some large polypeptides.

When I was researching combination products and the vast landscape of therapeutic products that are approved, this report stood out to me from the Office of Combination Products, or OCP. And if you look at the panel at the bottom left corner here in green, between CDER, CBER, and CDRH in the year 24, nearly 600 plus products were reviewed with a designation of combination products. So that's a large number. And as I understand, nearly 30% of all products fall in that category, give or take. And so that makes it very important to review the requirements for bioequivalence of these products.

Taking another step, and as an outcome of these research initiatives, and again, kudos to the agency for developing these product-specific guidance documents. There's a vast number of these, and I understand nearly 2,400 plus PSGs are now available. If you look at 2025 alone, a large number of issued either new PSGs or representative revised PSGs. And so nearly 200 plus were issued last year in 25. Now, I've listed some of these here. Not all of them are combination products. Some of them are simpler products. But again, you get the idea that there's a lot of headway being made in terms of either developing new PSGs or at the same time revising in a continuous improvement in these documents.

Let's look at combination products. A vast landscape of dosage forms are available. And going from left to right, you have transdermal drug products, TDPs, you have vaginal inserts, ophthalmics, which can be in the form of solutions, suspensions, emulsions, injectable products, again, a vast bucket there in the form of solutions. suspensions, liposomal products, let's include polypeptides there as well. And you can see this vast list here. Each one of these, they're associated with a PSG. And that's incredibly useful when developing

products because they can be wide-ranging in terms of technical complexity and the requirements to develop a genetic products next to dollar lead.

If you look at the in vitro analyses schemes that are listed in the PSG, again, this is a summary of high-level snapshot of what is currently called out for in different PSGs. Let's start again on the left here with transdermal drug products or TDPs. A common theme that you'll notice across a number of these There's this requirement for in vitro release tests, or IVRT, in some cases leading up to dissolution. If you talk about TDPs alone, there's adhesion studies, there can be whatever transmission rate for hydrogels. But if you look at a majority of these that are associated with some form of suspension type products, there's API characteristics. That may be related to a particle size distribution, PSD. They may be related to the crystal habits or the polymorphic forms, and some of the more simpler requirements in terms of viscosity or osmolality or pH.

If we take a special case here, not reading through all of this, if you go to long-acting injectables in AI, that's being a big focus for the industry. There can be some special analyses. If there's lipids involved here, there can be multiple attributes associated with lipid characterization. If there are polymers such as PLGA, then again, deep dive into the PLGA space. If there are emulsions, then there are globule size distribution. suspension of the sedimentation rate and volume. But long story short, a number of tools are currently available and utilized for such products.

If you go to polypeptides, again, that starts at the very basic in terms of the amino acid stitching, in terms of the polypeptide characterization, the content, the purity level, Again, this can go to certain spectroscopy techniques, such as FTIR, NMR, CD, and such, and leading up to more evolved physical chemical properties and glycination of those, can go into sacks and wax analyses, and then, of course, biological acid values. So without spending more time here on this, let's switch gears and go into another type of dosage forms, which is where I'll spend the majority of the time today, the rest of the time in this presentation. These are locally acting products and commonly referred to as OINDPs, sometimes also as OIPs. So orally inhaled and nasal drug products.

Again, different dosage forms fall in this category. You look at dropout inhalers or DPIs on the far left here. Solution meter dose inhalers, or MDIs, suspension MDIs, soft missed inhalers, as mist, nasal sprays, a large number of these. And then of course, inhalation solutions and suspensions, again, a large number of these. So what you'll see here, a majority of these are small molecules. There are some large molecules here as well. And each one of these is associated with a PSG, some that have been revised multiple times.

Again, coming back, analogous to the other dosage forms, coming back to the common theme here, what are the current in vitro analysis requirements as listed in the PSGs? So this is a snapshot of that again. Going left to right, one of the common themes, as you'll notice here, is this requirement to conduct single actuation content, or SAC, and sometimes delivered dose on the right side there as well. Another common theme that you'll see here is a very common technique called the APSD, or the aerodynamic particle size distribution, and within that, a specific fraction called the impactor size mass that is typically looked at. There's RAPSD, which is realistic APSD. I'll spend more time on that in the latest slides. Then there's dissolution, which is a common theme if you see from the other dosage forms, and then particle morphology, which is again another common theme from some of the other dosage forms.

When we go to the liquid dosage forms within OINDPs, there's some specific requirements there in terms of priming, re-priming, plume geometry, various spray characterization tools, whether it's duration, velocity, pattern, and such. But again, for the rest of this conversation, we'll focus on 4 techniques here. And let me start with that. So the rest of the talk is going to be a case study about characterization of a dry powder inhaler, and more specifically, a dry powder inhaler, which has two active pharmaceutical ingredients along with an excipient.

So the first technique that I listed here, which is part of the PSGs, is the APSD by cascade impaction. Again, this is recommended as in vitro BE tool. You'll see that multiple cascade impactors are reported in the USP <601>. Two of the most common types, I have some images here, the Anderson cascade impactor. and the next generation impactor. If you look at the requirement to characterize these, typically comes from the beginning and end life stage of the product. The flow rates that we typically utilize to characterize products is 30, 60, and 90 LPM, encompassing of the patient population. The typical volume of the air drawn through a delivery system is about 4 liters. When we look at all of these systems, the API is typically recovered from the entire system. And these can include different parts, such as the mouthpiece adapter, the induction port, a pre-separator that's utilized, different stages of a casket impactor and the filter. All of this is recovered and a mass balance value is reported so that we can understand the robustness of the methodology here. The simplistic primary data that comes out of this mass recovery is then further treated, and that can be utilized for population by equivalence analyses if there are two products being compared, a test product and an RLD. And more specifically, the impact of size mass, or the ISM, is compared between two products. In addition, there are certain supportive evidence values that are reported. These can be MMAD, GSD, and the fine particle mass, or the FPM.

So if I switch to a data slide here, these are some representative data that we have generated utilizing the PSG for a rapid inhaler. What you'd see on the top panel of the slide in blue is the API one. On the bottom panel of the slide is API 2. And you'll see three different plots for each representing 90, 60, and 30 LPM. On the y-axis, this is mass recovery. On the x-axis, these are different stages of the impacted system. In a more simplistic format to represent these data in terms of mass recovery, of course, we can conduct multiple other sophisticated analyses post-treatment of these data to then go into PBE analysis and then further take that to compare RLD with our test product.

Let's go to another tool, dissolution. We touched upon that. This was a common theme across multiple combination products. This is, again, highly recommended for in vitro BE studies. You'll notice that there are a variety or multitude of dissolution methodologies that are available. On the right side of the panel, I have certain representative dissolution bath systems, and there are multiple tools and techniques that can be utilized to conduct dissolution analyses. For OINDP products, typical life stage of analysis is the beginning of life. The dissolution data can be reported in mass units and also as percentage of the drug dissolved, if you will. A very important requirement for dissolution methods is that they need to be robust, they need to be reproducible. At the same time, they need to be discriminatory to be able to distinguish between the products, whether that's a result of the inherent raw material or a part of the process.

So a number of things that go into developing and validating methods of this type, that can be a preference selection, sample collection, process, the amount of the dose that's been utilized for dissolution, the media type, media volume, pH of the media, stirring and agitation rates, sampling times, and the list goes on and on and on. But essentially, the dissolution method has to be fit for purpose. A very common way to utilize dissolution to compare different products is the use of the similarity factor, or the f2 which the industry is fairly familiar with.

Let's again take a look at some data that we have generated for dry powder inhaler. Of course, in this case, the molecule that's chosen and plotted here is resolution rate limited. On the right side of the panel here, you'll see the API cumulative release values and percentages. You'll see time on the x-axis. And in this case, of course, we have different time points chosen along with the standard deviation there. A point to note is that this is not a fixed phenomenon here, or a fixed representation. The method has to be representative of the product that has been targeted. The time point selection, the selection of the conditions under which the release occurs and is developed, has to essentially simulate the RLD, and at the same time, it has to incorporate a very important factor, which is the clinical profile, the PK profile of the RLD. And so the effort here is to

develop an in vitro in vivo correlation, or IV-IVC. So this is again one of the very simplistic forms of representing these data further post-treatment can be conducted to again dive into similarities and dissimilarities between a test product and an RP.

Let's go to a third technique, which is particle morphology. This has been listed in multiple PSGs. Particle morphology can be utilized for multiple dosage forms, not just limited to OINDPs. This is not necessarily an in vitro BE tool, but more a comparative physical chemical, characterization tool. In this case, imaging comparisons are drawn. When it comes to OINDPs, the emitted dose fraction of the aerosol is utilized, it's collected, and then the API and the rest of the formulation can be characterized for particle morphology. Typically, beginning and end-of-life stages analyses are conducted. A technique that's gaining popularity is MDRS, that's listed here. That's because it provides specific morphology information in the sense that not only do you get morphology information, but you can also ascribe chemical ID with Raman spectroscopy. So that gives you two for one and that allows us to then go and take a deep dive into a number of phenomenon here on particle morphology of individual components, also agglomeration behavior.

So if you look at chemical classification alone, we can target the specific API, we can target a specific excipient and investigate that, but then also take a step beyond and look at 2 or multi-component systems. And look at agglomerated particles. So again, on this slide, there's some representative data on the morphology that we have developed for a dry powder inhaler. What you'll see here is that we've divided the chemical entities into 3 components, API one, an excipient one, and then agglomerates of an API one and excipient one. Not only can you target a desired number of particles as listed in one of the columns here, you can then draw a variety of information that can help you ascribe quantitative numbers to morphology.

We can go one step beyond and look at the microstructural composition of a formulation of a product. And in this case, we can look at the percentage of API one, percentage of excipient, and also the percentage of a combination of excipient and the API agglomerates, if there are any. This is what the raw data looks like. You have simple images that can be utilized to not just draw morphological information and you see images here, but then you also collect spectra and spectral overlays, which can then be further processed and lots of post-processing to then draw quantitative information and similarity or dissimilarity attributes between a test product and an RLD.

Finally, let's take a look at this technique that has again gained traction over the past two decades or so, is realistic APSD. This is similar to APSD, but in the sense that we are using realistic mouth throat models. We discussed cascade impactors earlier, and those still remain the same. However, the MT models can really in different formats. So you have

some examples here on the top. These empty models can represent different anatomical features. They can be small or large. They can be utilized with different breathing profiles of patients, weak or strong, depending upon the patient population. Typically, beginning and end-of-life analyses is conducted for the products. Analogous to the previous APSD discussion, the additional attributes and the masses, API masses collected on the mixing inlet and also on the MT models. Again, similar to the previous discussion, mass balance is collected, population by equivalence can be drawn on the impact of size mass fraction. And then again, supportive evidence in the form of MMAD, GSD, and fine particle mass.

These are again representative data that we have generated for a combination DPI. You'll see API 1 on the top panel, API 2 on the bottom panel in green. You can see four different plots here, the most simplistic manner representing these data, mass recoveries on the y-axis, different stages of the impactor system on the x-axis. You can see four panels here simply because the MT1 can be as small or a large, MT1 and MT2. Similarly, you can have different profiles, profile one and two, which can be weak or strong. And so that gives you a plethora of information across a patient population, which can then be treated, can be processed, and can be represented quantitatively to conduct a PV analysis.

So we reviewed some of these requirements of in vitro vectorization tools. Some of these are non-standard. Two or three of the techniques I described earlier are specific to OINDPs that are not utilized for other type of dosage forms. Things like dissolution, particle morphology are very commonly utilized across multiple dosage forms. So when we look at these techniques and evolution, I think we have come a long way through the various research initiatives, again, sponsored by the industry and also a large number of them sponsored by the agency here. There's been a dramatic improvement in the utilization, acceptance, and execution of these methods. Even so, we still see some challenges with the execution and implementation of these tools.

Number one is robustness of the technology, as you can imagine. Sometimes the technology is evolving concurrently with the product development. So the product, it can keep pace with the execution phase of product development. There can be development times because of this reason. Equipment uptime is a big topic. I mentioned MDRS earlier. Robustness of the laser source was a big deal for a good period of time in the past years. The second one is access to technology. There can be limited operational units for very specialized tools. Again, I use MDRS as a case study there. There can be limited capacity with the equipment vendors, limited capacity as CROs, and maybe the sponsors are unable to implement specialized tools or procure them in their own shop.

Development cycles can be long and tedious, especially when there are complexities involved around technology. It's one thing to use something as an R&D tool, as a one-off

analysis, another thing to use it, qualify that for a QC tool or for in metro BE purposes. So the time and effort required to qualify and validate these methods can be substantial. And which is where it comes to, again, this workshop here and the initiatives, there continues to remain a need to develop the tools and techniques that can act as alternatives to clinical studies at best case, and in the base case, at least supplement clinical studies such that we can have a robust and an accelerated development of generic substitutable products.

If I look at my own reflections here, drug device combination products or combination products as a whole, offer a higher technical barrier towards generic product development. There can be multiple reasons associated with that. Sometimes there's just clearly inherent technical profile of the RLD. The drug constituent part may be highly customized. Similarly, the device constituent part may be highly customized. Manufacturing technologies equipment train that may not be available broadly and may be bespoke. We touch upon the non-standard characterization tools. And then there's some practical elements around supply chain disruptions from the OEMs. There can be cases where the RLD performance may vary over the lifespan when such products are being developed. There may be IP aspects associated with that. But independent of all of these, I think the utility of the PSGs cannot be understated. They provide a very structured, predictable, and a consistent framework for developing such products. And within the umbrella of the PSGs, the in vitro characterization tools offer us an incredible opportunity to accelerate the development of generic products. And again, kudos to the agency for developing these and spending the time and the research initiatives there. And we intend to make the most of these, of course, ourselves.

And the final slide I have here is, this is the equation for me. We utilize a non-standard or advanced in vitro characterization tools. This can lead to predictable and accelerated genetic product development, which in turn can expand and potentially expand access to the genetic products. So again, happy to be here. Thanks for your attention and time, and I look forward to the panel discussion later today.

Panel Discussion

Andrew Babiskin, PhD (Moderator): Thank you for your presentation. While we bring the rest of our remote attendees up, I'll do the rest of the introductions for the panel. I'll start with who's in the room from the non-FDA side. So immediately to my left, we have Mr. Brandon Wood from Teva Pharmaceuticals. He's an accomplished regulatory affairs leader with 15 years of experience in the pharmaceutical industry, specializing in complex generic drug development. As A Senior Director of Regulatory Affairs at Teva Pharmaceuticals USA, he leads regulatory strategy submissions and lifecycle management for complex generics.

And then on Brandon's left is Dr. Andrew Cooper. So you may not see his name on his agenda. He was kindly volunteered to participate also in this session and also in the, he also will be in the following session. So Dr. Andrew Cooper, current role is respiratory bioequivalent strategy lead in Viatris R&D. Based in based in Sandwich, UK, his role has been fostered on focused on respiratory product development for around 20 years.

Okay, then for the people on line, we already introduced the speaker, Dr. Gupta. Next, we have Dr. Tausif Ahmed from Mankind Pharma. He's currently working as the Senior Vice President and Head Clinical Research in Biopharmaceutics Development at Mankind Pharma Limited. In India, he is responsible for managing all bioequivalent studies, preclinical toxin phase one to four clinical trials supporting global complex generic drugs. and NCE slash MBEs at mankind. Next, we have Dr. Allison Dunn from the University of Maryland School of Pharmacy. She is a research assistant professor at the University of Maryland School of Pharmacy, an investigator within the Center of Translational Medicine. Her research focuses on pharmacometrics and model-informed drug development with applications spanning clinical pharmacology, regulatory science, and complex generics.

Yes, that's everyone. Then now from the FDA side, we have Dr. Priyanka Ghosh. She is a lead pharmacologist within the Division of Therapeutic Performance II in the Office of Research and Standards, Office of Generic Drugs. Her areas of expertise include products dose on the skin and other mucosal tissues. Then we have Dr. Myong-Jin Kim. She serves as the Director of the Therapeutic of Therapeutic Performance II within the Office of Research and Standards and Office of Generic Drugs. Sorry, I think I may have said Division of Therapy Performance II for Priyanka. It's Division of Therapy Performance I. MJ's division largely focuses on bioequivalence approaches and bioequivalence standards for world drug products, and also subject safety considerations and in Vivo BE trials.

Next, we have Dr. Bing Lee. She is Associate Director for Science in the Office of Bioequivalence within the Office of Generic Drugs. In this role, she provides scientific leadership and expertise in assessment of bioequivalence studies submitted through ANDAs and oversees the scientific initiatives within the Office of Bioequivalence. Next, we have Dr. Pahala Simamora. He serves as the Director of the Division of Product Quality Assessment IX within the Office of Product Quality Assessment II within the Office of Pharmaceutical Quality at FDA. His division oversees the quality assessment and regulatory submissions under both the GDUFA and PDUFA programs.

Next, we have Dr. Lei Zhang. She serves as the Deputy Director of the Office of Research and Standards within the Office of Generic Drugs. She oversees the GDUFA Science and Research Program to assure the therapeutic equivalence of generic drug products. And I believe that is everyone. So with that, I'll turn it over to my co-moderator, Dr. Yan Wang, to

start the panel discussion. Oh, and also as another mention, yes, there are microphones in the room, so if there's people have any comments during a discussion, please feel free to go up to them and to those and those of you online if you do have comments if you are looking at those as well.

Yan Wang, PhD (Moderator): Thank you, Andrew, and thank you, Dr. Gupta, again, for the very comprehensive yet concise summary. I think you laid a great ground for us to kick off today's panel discussion. I think as the presentation highlighted, for many complex dosage forms, we were, through the research, we were able to introduce either totality of evidence-based in vitro only approach or in vitro in vivo combination approach. Those currently in the in vitro characterization list is very comprehensive. But at the same time, when we have more studies, we do recognize that means you could have a lot more studies to validate. potentially higher chance to failure. And also another thing is when we recommend those approaches, as of now, in many cases, the precondition is the proposed generic formulation should be quantitatively and qualitatively the same, Q1 and Q2, the same. Or for a certain area like topical inhalation, no major differences. So those could be potential constraints from a product development standpoint. So the first focus today, we would like to obtain industry's feedback as well as our FDA folks' comments is to better understand the current thinking whether you know there is a need to further understand formulation design space and the recommendation is on image characterization relationship with clinical performance, with the vision those could potentially lead more flexibility in formulation composition when trying to establish bioequivalence using in vitro only approach or in vitro in vivo combination. And those also could potentially help to develop a risk-based classification for categorizing post-approval changes to support lifecycle management. So I'll stop there to see this visionary questions if our industry folks would, and also our academia colleagues would agree with that. Is that on the right track? So, we can start. With people on, yeah, Brandon, please go ahead.

Brandon Wood, BSc: Yeah, hello, this is Brandon. Thanks, Yan. I think, you know, generally speaking, absolutely. I think more flexibility is key, and in general, you know... Dr. Gupta walking through his presentation and your summary there, I think what's really important here is not less rigor, but smarter rigor, right? Like what are the real levers in terms of clinically meaningful differences? So any move towards more flexibility, more in vitro only or in vitro compounded approaches, I think are strongly supported by industry. And I think one of the key points is, you know, as we're developing research and, you know, moving this initiative forward, it's really important to understand the scientific rationale behind the underlying thinking for why something is clinically meaningful or clinically not meaningful, because that will allow us to ensure that the research is adopted in a very efficient and effective way. And, you know, we're already reverse engineering a product. We don't want to

reverse engineer expectations as well. So generally speaking, I would fully, you know, agree that, you know, additional flexibility would be very useful there, especially in certain product types where we're already really focusing on, you know, in vitro approaches or Q3 characterization approaches. I think respiratory implants, you know, certain complex APIs are really ripe for, you know, additional flexibility right now.

Yan Wang, PhD: If you have anything to add, go ahead please.

Andrew Cooper, PhD: So I got a sort of slightly nuanced answer for this question, actually. I mean, I think the first point is that, you know, different dosage forms and routes of administrations are in different places in the PSGs, and so I don't think there's a kind of one-size-fits-all detailed approach, but clearly the direction of travel towards flexibility is is a good thing from an industry perspective. But I think my little caveat is that sometimes the certainty that comes with a Q1, Q2 sameness requirement together with a clear and facile pathway is actually advantageous. If you're comparing that to uncertainty associated with the alternative pathway. So I think we're, you know, we're quite keen that unless there's a really, really clear pathway established for justifying Q1, Q2 differences, having the option to stick with Q1, Q2 sameness is something we would want to retain. And I'm told by my colleagues that in locally acting GI peptides, for example, you know, that option exists. And we've found it actually advantageous to stick with that sometimes, because then you get into a kind of dissolution only based BE. So that's my little caveat.

Then when we actually come to looking at flexibility, I think the phrase risk-based has already been mentioned. And the kind of approach that we would want to follow is very much a kind of understanding design space, risk assessment based approach, where you're looking at the impact of differences or changes on the CQAs, which arguably could include the in vitro, the sort of complex in vitro BE end points that we now may have. And then you're also needing to consider the kind of risk that those in vitro tools and possibly in vivo, in the case of respiratory, it's still largely in vivo as well, are going to be sensitive to the impacts of changes on local equivalence. And I think in that sense, I wouldn't personally think that what one necessarily needs is a kind of well-established IVIVC. I think sometimes that it should be possible to take a kind of fairly common sense approach where you're looking at the potential impacts of differences and you're using all the knowledge that exists. You're using, you know, very maybe very specific literature, using understanding of in vitro vivo relationships, but maybe also you're just making sound scientific reasoning based on physical chemical principles. And I think that, you know, that's that approach, I think, should be, should be followable, if you know what I mean.

And I very much appreciate Dr. Gupta's presentation in kind of laying out where we are with the respiratory products, because that's my area of expertise. But I think we are seeing

there that, you know, we've now got essentially 2 pathways. We've got a Q1, Q2 sameness or similarity pathway, which… we, sorry, I said the wrong thing. We've actually got a pathway for Q1, Q2 difference that's now, which is actually the traditional pathway involving a clinical endpoint study. That might be useful in certain circumstances. But then we've also got some flexible language around Q1, Q2 differences, which can lead into that risk assessment approach. And of course, for respiratory products, because we generally have an in vivo endpoint, that does, I mean, if you kind of get to the point where there's still residual risk after the in vitro studies, sometimes an in vivo PK study, I think, can help to address those residual risks, and that's preferable to doing a clinical endpoint study in a lot of cases. So I think we're already in quite a good place for respiratory products. I can't speak quite so much to other product types, but the general direction of travel I think we support, but we do need to retain flexible flexibility, if you see what I mean. That, you know, that what we don't want to be pushed into is a position of uncertainty as to whether something's going to be acceptable. And having Q1, Q2 sameness as an option with a simple pathway is something we definitely want to retain.

Yan Wang, PhD: Thank you. Then switch to our online panelists. Dr. Tausif, if you'd like to go first.

Tausif Ahmed, PhD: Thank you. I think, very valid points. I just want to touch base on one aspect, especially for ophthalmic products. I think from an industry perspective, the guidelines and the PSGs are very clear. If we are Q1, Q2, we can go with a waiver, but in certain cases, the difference in Q1, Q2 is so minuscule. And for that, it kind of requires, yes, agency has been very supportive in giving feedback on what approach to be taken, but the challenge we face is that there is no clear direction available if we are deviating from the reference, especially from an excipient which has been used very commonly in other products, whether we need to do a clinical endpoint study, because doing a clinical endpoint study, especially in conditions like dry eye disease, where the variability is exorbitant. So, and placebo itself has an effect. So I think those are the scenarios where we need a little bit more guidance and more clarity and more engagement with the agency. If we're talking of research, the way agency has been doing research in terms of some other products where role of permeability enhancers has been studied. On similar lines, if some research can be focused for the ophthalmic products, it will really help industry.

Yan Wang, PhD: Thank you for that feedback. Then, we'll go to Dr. Dunn.

Allison Dunn, PhD: Hi, yeah, I agree with everything that's been said so far. I don't have too much more to add than that. I agree of flexibility is important. I work more on the clinical side rather than the in vitro formulation design aspect, but particularly flexibility where the

clinical risk is much lower seems like a very good place to start. And it's just going to, like everything, end up being a risk-benefit analysis.

Yan Wang, PhD: Thank you, and last, Dr. Gupta, if you have anything to add in addition to what you discussed in your presentation.

Abhishek Gupta, PhD: Sure, maybe I can add a couple of things there. I think if you see the common theme here, the word flexibility, risk-based approaches turns out. I would like us to go maybe upstream in the design of, in this case, a generic product. I think the flexibility on the Q1, Q2 side, which is very clearly laid out and the industry has been using that for quite some time. I think the word fit for use and fit for purpose in context of the RLD would be very useful there. When we look at Q3, I think there are a variety of tools that are part and parcel of the PSGs that are currently listed. But it's sort of a carte blanche. Not all the tools may be applicable in each of the cases. So I think some level of customization flexibility would be very useful.

Number 3, I would, in certain cases, let me draw attention to, let's say, OINDP studies where PK studies are conducted. And then, of course, you have an option to conduct pharmacodynamic PD studies also. Here the challenge is that you have a patient interface and a number of other products, you may not have a patient self-use interface also. So you have some very complex systems, which in their entirety may be different in individual constituent parts, whereas a system may perform very similar to the RLD. So I think that is all the more reason to build in the flexibility early on into the system.

One of the things I would draw attention to is also these complex dosage forms when you conduct, let's say, PK studies, clinical output. There can be a variety of challenges in conducting these. It can be limited to the RLD, it can be variability of the RLD, also the complexity of these systems inherent nature of the use in a clinic. So I think pooling of data through multiple PK studies and combining and utilizing the in vitro tools, Q3 and such, would offer a very viable pathway, let's say a pragmatic pathway, to seeing more genetic products. Let me just pause there.

Yan Wang, PhD: Thank you. Now, I'll see if any of our FDA colleagues have anything to comment, not on the potential solutions, more along the line in terms of the gaps or anything visionary.

Priyanka Ghosh, PhD: Maybe I have a question for our industry panelists. I know Andrew mentioned that having the having Q1Q2 sameness definitely helps because there is a straightforward regulatory pathway there. But in the with the new legislation in place related to Q1Q2 sameness, What kind of, like, what are some situations where you may

want to go beyond Q1 and Q2 or would like to explore Q1 and Q2? And what kind of research do you envision us doing in that space?

Yan Wang, PhD: I think this is an open question for anyone that has anything to say.

Abhishek Gupta, PhD: Maybe I can take this one and add and sort of reiterate what I mentioned earlier. Again, focusing on drug device combination products and within that umbrella, taking a subtype for orally inhaled and nasal drug products. You have a drug constituent part which can be designed as Q and Q2, but at the end of the day, what comes out of a device, the single actuation content, the deliver dose, is highly dependent on the device as well. And devices, no two devices come alike. They may have similarities in the use and the label, but the inherent design may be different for a variety of reasons that I described some of them earlier. In that scenario, the goal is to have a performance X device, X actuator in the recipe world as we call it, and flexibility in the Q1 and Q2 that accommodates for that variability, leading to the same end result, the same end performance to the patient. and that flexibility would be very useful. And then again, that depends on individual scenarios and individual products. So it would be a little difficult to focus on one product type here, but I can clearly see that as one scenario where flexibility in Q1, Q2 could be very useful.

Andrew Cooper, PhD: Yes, I certainly agree with that point from a respiratory product development point of view. You know, I think we're encountering other reasons why sometimes we have to or feel that we need to deviate from Q1, Q2. I mean, IP can come into this because quite often there are some very specific constraints around formulation components in patents that, you know, that we have to work around. And of course, there is a really big example out there in the respiratory space at the moment, which is propellant change, where, you know, we're essentially legislative and commercial context changes are driving what on the face of it appears to be an enormous change in the product where you're having to change something that's 99% of the formulation. Now, I mean, the impact of that's interesting because the thing you're changing actually is actually probably not really part of the formulation by the time the drug actually deposits in the lung, it's a gas, basically. But it does create quite an, you know, that's a scenario that I know that we're working with the agency quite actively to get a clear pathway for, but it's quite a spectacular example, shall we say, of Q1, Q2 difference in gross terms, anyway.

Brandon Wood, BSc: This is Brandon. I would just add maybe one example on a different dosage type, but, you know, I think implants are another topic where it comes up. You know, even with the legislation which was passed, which, you know, is really a game changer, to be honest, in terms of Q1, Q2 determination, manufacturing processes can have a huge impact on the finished product, right? So there may need to be some specific

formulation differences to account for the specific manufacturing process to enable a finished product that will perform in the same manner and really no clinically meaningful differences, but just maybe another, you know, curveball in terms of where it might be applicable.

Yan Wang, PhD: Yeah, Thank you.. and I think Dr. Cooper, oh, we have a public question and comment

(Audience Member 1): To build on Brandon's comment, in the manufacturing space, what kind of research would assist both industry and perhaps the regulators in addressing some of those concerns?

Brandon Wood, BSc: Yeah, that's a great question. And to be honest, I'm not sure I have a great answer. I think what we see, you know, in the implant space specifically, a lot of the manufacturing equipment is bespoke. A lot of the manufacturing processes are quite novel, right? So it's hard to kind of template that out to a point where it's, you know, more commonly used. Perhaps you can go into specific principles, overall principles, and breaking down the manufacturing process into, you know, key individual elements in terms of critical parameters where the equipment isn't necessarily the main focus, but the process itself is. That might be one recommendation, but I can say, you know, in that space, a lot of the equipment is incredibly bespoke, so it's a bit difficult to, you know, focus so much on the equipment, maybe a bit more top level on the process.

(Audience Member 1): Does that include changes in manufacturing processes, such as going to continuous manufacturing? Are generic companies pursuing that avenue as well in manufacturing products, and this could include oral formulations as well, potentially.

Brandon Wood, BSc: Yeah, absolutely. I mean, you know, I can just speak for myself here, but it's, you know, always something that that's evaluated. Obviously, there are a lot of economical concerns in the generic space right now, so that can prove to be a bit challenging, but you know, we'll never stop evaluating potential improvements and you know, continuous processing, general, you know, incorporation of improvements. So certainly under evaluation, but, you know, to be honest, there are some economical constraints within the generic space to be able to fully get them online.

Yan Wang, PhD: Go ahead please

(Audience Member 2): Thank you, Dr. Ghosh, for asking that question regarding Q1-Q2. I think we have now come to a point where we need to evolve beyond the Q1-Q2 and perhaps focus a little bit more on the functionality of some of the excipients that contribute to the Q1-Q2 sameness. For example, in topical dosage forms, the viscosity or rheology, a Q3 component is far more critical, for example, the residence time or penetration of the

active ingredients. And therefore, some flexibility, as Brandon and others have spoken about, is critical in the Q1-Q2 space because it's very tight. And it's not necessarily as clearly understood as to why, for example, the 95 to 105, et cetera, numbers are critical. We have already seen the FDA take a stand on that with respect to the buffer components and the buffer capacities with respect to some of the ophthalmic solutions and suspensions. And perhaps that can be extended to viscosity modifying agents too, such as whatever the components may be, the hydrogels or in the lipophilic components. So my suggestion is to take it a little bit one step forward. And provide more guidance on what you expect from the product, rather than focus only on Q1 and Q2. Thank you.

(Audience Member 3): I have a question regarding the Q1, Q2. Yes, the legislation has passed. It's a great win to the industry. But I do have some things, and I think Andrew picked up a little bit where when we have patent issues, and that becomes a little harder one. To win, I was looking at if the agency can consider sometimes these, because of the patent and you come around with the patent, you do choose some other inactive ingredients where those ingredients may have used globally in a same route of administration, if the agency can consider that, would be also very, very helpful for the industry to overcome the patent issues. Thank you.

Myong-Jin Kim, PharmD: And I really like the comments that we are receiving from the audience. I have like 15 years of new drug experience at the FDA. And what I really observe is cannot think outside the box or the framework that we already established and try to work or come up with solutions within that box. I personally don't like it. So when you post a questions about the or comments about the Q1Q2 aspects, can we go beyond that Q1, Q2 and consider the importance or the in on importance of the or less importance of the inactive ingredients or the formulations. And we have so much of data, so much of knowledge from the new drug development. And I focus so much on the life cycle management because we have all this information. So what I like to hear from the audience, as well as the industry colleagues, is that what can we do differently and go beyond that inside the box thinking, what can we do differently? And the excipient, or even the oldest information that we have gathered already, and how can we go beyond that? I would like to hear from that so that we can focus on that research.

Bing Li, PhD: I also want to add some thoughts about the inflation drug product Q1, Q2. I think at the beginning for inflation drug product, the Q1, Q2 recommendation was to fulfill two purposes. One is to ensure a product that is in formulation wise is similar to Q1, Q2 to the reference product to ensure that there is no additional local toxicity, local irritation that caused by a non-Q1-Q2 product. Okay, so that's the first sort of behind, behind the scene recommendation for Q1-Q2. The second one is more, maybe more important is to ensure

the drug performance with a Q1-Q2 product will be equivalent. So I think if these two underlying reasons that supported at the beginning supported the Q1-Q2 could be resolved through the research, through the performances, that the Q1, Q2 recommendation can be removed from the package. Actually, was the new, you know, propellant, propellant, new generation propellant, it is a challenge. It comes to our challenge that we have to think about a non-Q1Q2 for inflation drop product. Thank you.

Yan Wang, PhD: Thank you very much for the very insightful discussion. If I may summarize up to this point.. oh sorry, we have another comment. Go ahead please.

(Audience Member 4): It's a very good comment. For us as industry, it's very important to understand why some concepts are laid out in the PSG. And I think we will afterwards talk as well in the panel 5 discussions. So we need to best understand the current agency thinking. and explanations like that easily accessible for all of us, why there is Q1, Q2 for a specific dosage form. It would help to understand why can we deviate then with a good justification, because in the end the PSGs are guidances and helped us and we have forums like PSG Telecoms, we have pre-ANDA meetings, we have product development meetings, to exactly discuss this, but to very clearly know what is the current thinking, why a test is there, why not a test is there, why Q1, Q2, Q3, and this could be very different for OSD vs respiratory products that would really help to know and to better develop the products.

Yan Wang, PhD: Thank you for that comment. So, given the time, I will summarize the first part of our panel discussion, just to, you know, make sure we have heard most of it, and please feel free to submit your comments to a docket or talk to us offline. So, what I heard so when Q1Q2 is feasible without no constraint, then it could be still advantageous. But even when you are Q1Q2, it doesn't mean you will hit all the Q3. So what I hear, the underlying question here, beyond just the Q1Q2 to allow more flexibility in raw material choices, is to really understand when in vitro only approach or in vitro is part of BE assessment. To understand the scientific rationale more clearly on our recommendation in terms of that would guide you when what would be the room you can deviate and when you do see a difference how, what would be the direction for you to justify those differences to support your product. So I think from a research perspective, we certainly could do more paper research to, as MJ mentioned, we have a lot of public domain information, our own research. We could go through those to more analyze and summarize and share those outcomes. through a proper venue and in terms of the web lab research for certain particular dosage forms, we could further explore and have more papers to describe our scientific rationale and thinking in terms of why this particular Q3 may be relevant and how it may impact the clinical performance. And another key thing I heard, I think Dr. Cooper

mentioned, is when we're trying to make those clinical relevance, we probably could put aside the classic IVIVC mind, although that's always the desired, but not necessarily the only way to achieve that. So what we can achieve is really through comprehensive physical chemical characterization, knowledge, formulation, design, manufacturing, control, all those things will link and bridge into clinical performance. So with that, we have many other really important topics, so I'll pass the podium to Andrew to continue the discussion. Thank you.

Andrew Babiskin, PhD: (inaudible) ... Sorry about that. All right, our next topic is enabling generic development approval when the RLDRS are not available or very limited availability due to practical challenges. So let me explain that a little bit more. So the first case where the RLD/RS is not available is a bit more self-explanatory. It's just that this product has either no generics in the market and the RLDs is continued, or even if there was generics, there's just nothing remaining on the market anymore, but you're looking at a way to bring that product back to market. But the second category, with the very limited availability due to practical challenges, this can come from just not widespread distribution of the lots from the manufacturer. And so that could become a challenge, especially you need to use them for very large scale in vivo studies, or even for in vitro approaches where you need to characterize multiple lots. And then that could even be further compounded if even procuring that product also comes with great expense due to the high cost of the product. So these are all the scenarios that we want to capture within this category, and what type of like scientifically justified approaches that can be enabled to enhance product development and regulatory assessment, and some of these cases based on either like historical PK data, clinical benchmarks, or comprehensive CQA characterizations of the legacy product. So I'll start with the first question here to ask to the industry. What are practical challenges that may lead to a no-go for product development? As an example, is it a large sample size of the RLD that's needed or its very high cost? Or the lack of available historical in vitro and in viva data, especially if you're considering to bring a product back to market; it's no longer on the market.

Hey, Brandon

Brandon Wood, BSc: Yeah, thank you, Andrew. This is a real challenge. This is a real problem. And I think what speaks near and dear to my heart is when RLDs are, you know, simply not practical. Whether the barrier is simply availability, cost. I will say at times, innovators go through great lengths or go to great lengths to, you know, to avoid, you know, providing product to generic applicants. And that can create some challenges. We have some tools, right, but even those can create inherent delays. But I think where, you know, RLDs are incredibly high cost, you know, I have a number of examples where you know, to

facilitate the PSG requirements as written, we would need to spend 10s of millions of dollars in RLD cost alone. And the reality is that the development never gets off the ground for that same fact.

So, you know, I think some areas that could be helpful in terms of addressing this issue are, one, evaluating ways that we can reduce either the sample size, the number of batches, or enhance analytical methodology such that very small amounts of samples are required for analysis. I think those are a couple, you know, areas that can go to great lengths. The other one that I know is a bit more controversial is, you know, we need to have an ability to at least consider foreign reference products within the scope of our development. I think that would be, you know, just as much of A game-changer as Q1, Q2 legislation, if not more. You know, even if it's to a point where, you know, the primary data is on the US product, albeit at maybe a reduced sample size, complemented maybe with a comparative foreign reference product. I think that would really help us to navigate that real challenge that, you know, at the end of the day is stopping generic development and innovation.

Andrew Babiskin, PhD: So with the foreign product, is that also just a current strategy that you undergo that you'd initially, in these cases that you initialize development with the foreign product, but then when you need to, you switch over to the US?

Brandon Wood, BSc: Yeah, no, exactly. I mean, you know, when we encounter these situations, we'll start early development. It'll also depend on whether or not it's a global development. But we'll start early development with a foreign reference product, establish a QTPP. And then when we start moving into more of the primary pivotal studies, we'll move over. But still, even there, I will say that that presents its own challenges, just, you know, getting the product at times is another reason that we might want to start with a European reference product if there are constraints or delays in having access to the US product. I think another area we see is with, you know, orphan drugs as an example, it's very possible that an innovator will just manufacture one lot a year, right? So then trying to get some batch variability, trying to, you know, understand the real ranges when we're implementing these wonderful Q3 and in vitro approaches, that in and of itself, you know, can take three, four years just to get a sample set that we're confident in. But yeah.

Andrew Babiskin, PhD: and another, sorry, and another follow-up question there, which would be to anyone that speaks here, like what type of products you think are the highest risk in this category? I already heard one, which is the orphan products, but maybe more specific on product category.

Brandon Wood, BSc: I would just generally say complex API. I think that's where I see this, you know, most rampant at least. You know, again, economically, I hate to keep going to

that point economically, but it's a reality, right? You know, sometimes the cost alone is prohibitive to enable generic development, even for the biggest companies.

Andrew Babiskin, PhD: Great, Andrew.

Andrew Cooper, PhD: Yes, I would like to raise sort of another aspect of this challenge, which is when we're looking at underwriting post-approval changes. And I think, you know, philosophically, it's sort of easy to kind of imagine the RLD as something that sits in a glass case, and it is, and it always has been, and it always will be. And what we find, I mean, I'm not really talking specifically from my own experience, but certainly from across other dosage forms, we find that the RL, well, the RL is a real product. You know, it has variability. And it was maybe approved a long time ago. Maybe the specifications are not particularly relevant to clinical performance based on current knowledge. And so, you know, we find that we're going back to a reference product or maybe the reference product has become unavailable. It switched to an RS in that scenario. And so the kind of bioequivalent standard doesn't seem to be as fixed as you would hope it to be. And in the worst case, you're in a position where you're actually having to reformulate your own product to reestablish bioequivalence. And that's been triggered by a post-approval change, which in itself we don't think is actually impacted by our equivalence. What's actually forced us into a reformulation is an apparent change in the reference product. And you know, I appreciate that there are sort of legal constraints on this, but as Brandon suggested around the use of foreign reference products, I think that it would be good if there was a more of a kind of weight of evidence approach rather than regarding the reference, the RLD or the RS as a fixed point. Regard that as part of the weight of evidence that says, is this change really having an impact on the bioavailability of the product? And part of that is actually comparison to your own existing product, which is an experiment that's very much easier to control than going out into the market and buying reference product. And so I think we would like to see, you know, some more flexibility and the agency being willing to draw on a kind of broad range of evidence around changes rather than being absolutely fixed on the reference product as it now is.

Andrew Babiskin, PhD: For clarification, like in your situation, you're talking about, you're talking about… during your own development when there's a change in the RLD profile.

Andrew Cooper, PhD: Yes, that's right. Or obviously it could be post approved.

Andrew Babiskin, PhD: Or even post.

Andrew Cooper, PhD: The classic one is probably manufacturing site.

Andrew Babiskin, PhD: You have to do comparison back to the RLD at that stage. Okay, yeah. Got it.

Jim? Yeah.

James Polli, PhD: Jim Polly, University of Maryland. Maybe I'll direct this towards Brandon, since you were talking about, you know, the suggestion that maybe you don't need as many reference lots. Sounds like there's a cost to doing that, and you see some advantage of reducing that cost makes generics development more viable. In practice, what gets lost if you were to only look at, let's just say, one lot? Do you think that would ever really matter? Just kind of curious about what practical impact that could potentially have that idea.

Brandon Wood, BSc: Yeah, so I mean, the big downside, obviously, is not having an ability to see the variability of the RLD, right? So, you know, to Andy's point, you know, we do see a lot of variability in reference listed drugs, and you'll never get a good picture. Honestly, not just one, but sometimes 3, 5, 7. You know, it's 10s of batches that you need to enable testing to generate those ranges in order for your product to, you know, fall within the range. You know, you're comparable, but one batch will never be suitable for a complex product. And that's part of the challenge. That's why, you know, at least for me, I also really focus in on the analytical method development, right? Like if we can use less sample, then in totality, we'll need less samples to conduct the development process. So I think that's one area you know, there's a number of products where the fill volume, you know, is less than a mil, right? So practically, in the analytical sense, that's going to create a huge issue. So I don't know that reducing the number of batches completely, it's balanced, right? Because we still need to see variability. We still need to understand that design space, that range. But at the same time, the balance is working off of the economical sense of what can we actually do that would enable us to select this for development.

James Polli, PhD: Can I just ask you a follow-up question? Like, I'm just curious, are you happy when you see variability? Does that mean it's going to be easier to show similarity?

Brandon Wood, BSc: It depends on the process.

James Polli, PhD: The obvious question, I mean, is this variability because of your lab's ability, or is this something you think is seen across different developers?

Brandon Wood, BSc: Yeah, so I mean, within lab and across lab, you know, it would be generally within the precision of the method itself. But when we see variability, I think there's two different ways. It depends on what area you're looking at. Variability maybe in a Q3 characterization parameter is a good thing at times, because then you have a wider range to fall into. variability in ISM, you know, when you're preparing for a pivotal in vitro bioequivalence study is not always a great thing, right? So I think it depends on the specific parameter you're looking at and the context of the product.

James Polli, PhD: Thank you.

Lei Zhang, PhD: I want to make a quick comment. I know you share a lot of challenges and would like to have the regulatory flexibility. I also want to remind you this is a research workshop. We need to come up with what the research we can help address those challenges rather than saying, oh, we need to change regulation. I wish we could, but on the other hand, within the current environment, what we can come up with the right research question to address those challenges, I think that will be very helpful. And I also want to remind you, FDA has recently have a docket open, talk about post-marketing changes, SUPAC, so you can feel free to submit your comments to that docket on what FDA's guidance should change, should enhance. I think that's a good opportunity. And also, I know you want more options, flexibility in the PSGs. Recently, we also do have include more options in our PSGs revision. I hope that does help address some of your challenges you may be facing, especially initially our PSG developed to assuming there's available RLD or RS, but that's not always the case. We do have a few PSGs revised recently to include the options when the RLD/RS is not available. I hope this is the right direction we are leading towards and also we hope we have more research can support those PS recommendations. Thank you.

Markham Luke, MD, PhD: Markham Luke, Office of Genetic Drugs. So one question for the industry folks. As you look at new drugs when they come into market, are you, and be mindful that perhaps you need those Q3 characterizations, but also thinking that some of those products might come off the market and you might not have availability. Are you characterizing those products and recording them as they come onto market? Is that something that industry is interested in doing? And is that something that you might see FDA have a role in? It's sort of like rapid throughput for Q3 characterization for products as they come in the marketplace.

Andrew Babiskin, PhD: Does anyone online want to comment on that or even just have a general topic?

Abhishek Gupta, PhD: Andrew, I can go and add maybe more broadly, not specific to this question only. I think you pointed out the challenges with availability and the availability of the RLDs. Some of these points have been spoken, but if you look at the current PSGs, the expectation and that has evolved in the right direction, I think, is to utilize, let's say, three RLDs. If you're conducting a PK and a PD study together, it should be the same RLD. If you're conducting a PK and in vitro BE using analytical tools, it should be the same RLD. That clearly poses a challenge, right? Because the constraints are, we'll leave aside cost for a minute. The act of collecting API or the RLDs from the open market in sufficient quantities to satisfy in vitro characterization, PK studies, and have retention samples both in the clinic and for skin can be a daunting chance.

Now, we look at the variability of the RLD, and I hear the comment around the variability somewhere useful, but when it comes to PBE analysis that I was describing earlier, a 90% CI, a 95% CI would simply be challenging if you have three different, very different RLDs along with three different test products. So I think one of the mechanisms that could help here is again, to go product specific, maybe decouple the requirements to have the same RMDs for the variety of attributes that I described earlier and look at the implications. Maybe one of the research initiatives could be to look at the implications of this. and come up with a more practical way of decoupling the same RLD requirements across the board. That would help. Also alleviate some of the requirements to study and investigate the RLDs or the test product early in their shelf life, later in the shelf life, which only compounds with a number of requirements.

Andrew Babiskin, PhD: Anyone else?

Tausif Ahmed, PhD: Andrew, I just have few few comments. I think a couple of points have already been discussed. I'll just reiterate special some cases where the there is no RLD, there is no reference available and the product has been withdrawn or the brand has withdrawn long time back. So there is no historical in vitro data available, in vivo data available. I think one point which has been discussed is use of a foreign reference product. I think it has its own legal implications. But recently there was a CRCG workshop and FDA presentation. I attended one of the FDA presentation. and that they'd given very good insights about different scenarios. When there is no RLD, no reference available, you could always, you can even develop a solution formulation, do the BE against this. So I think that is something that kind of research or some publications from FDA side. would really help the industry because even if we go and look into in the extreme case, you have to do some clinical study. But if there are multiple indications, it's practically impossible to do the clinical trial for every indication. So that's practically ruled out. So in terms of products which are very old and I have like personal examples where we have faced those challenges that they have been withdrawn 15, 20 years more than that from the market. There is no generic, there is no obviously if there is no reference, there is no RS, no generic is available, but companies want to enter into the market and there is no clear way forward. So I think some research, some guidance on this would definitely help. And I recall there were all close to 200 such products where the, which falls under different categories, where these different scenarios are available. So in short, what I want to kind of give the feedback from an industry perspective is if some research, some publications or case studies, how to approach under these conditions will really help and obviously the industry wish list is towards harmonization where we could use the foreign reference products. So I'll still mention that. Thank you.

Andrew Babiskin, PhD: Does anyone else want to comment on this? Note, we do still have 15 minutes, so we'll be able to touch on our topic.

Andrew Cooper, PhD: Yeah. I feel obliged to kind of respond to a couple of challenges that have been thrown back to industry here, but I have to acknowledge that I'm kind of running slightly unprepared specifically. So I think that, but maybe the two questions are linked, I think. There's the question of what research can be done, and then there's the question of of what we do on new drugs. So I think the first point to make is certainly within my own experience, getting our hands on reference product, getting our hands on foreign reference product and characterizing it as an early point in development is is very critical for complex product development. So we will certainly do as much of that as we can. And then, I mean, I can think of a specific situation where we do, for one of the products we're working on, think that there's a risk that the RLD could be withdrawn. And so what we're doing there is we're generating comparative data on what we perceive to be the likely RS that would then be established if the RLD was withdrawn. So we are, you know, attempting to kind of give ourselves the strongest possible position, both in understanding the reference product and in kind of dealing with risks of availability.

But, of course... New drugs are not necessarily and typically characterized using some of the complex in vitro tests that we use to establish bioequivalents. And so a kind of suggestion for research would be that four key products, and that's where I kind of run out of specifics, if I'm honest. You know, if the agency was to sponsor research to kind of generate a baseline set of data with some of these complex characterization tools that then becomes kind of publicly available, it's there as a reference point against changes in the reference product or non-availability of the reference product. You know, that would actually be, I think, quite useful to industry. As I say, what I can't really do is tell you right now what those products would be that we would be particularly interested in, but I think that could be something that maybe could be a subject of further discussion.

(Audience Member): Just a quick comment regarding unavailability or limited availability of RLDs. So the question is, sometimes the products are manufactured 1 batch a year. Your requirements are three lots of RLD versus three of test in an in vitro characterization study. It's difficult to get access to three lots. And so to your question, what can FDA do to guide us is, okay, in that case, can we run the study with two? Would you allow or can you recommend any statistical parameters and changes of flexibility there? Again, the same question of flexibility comes up. This can we be more flexible in how we interpret the results and data If I only have two logs, or if I only had one log. In spite of the fact that, of course, we like to see more variability at times, but if it's limited availability, what do we do? Some guidance on that would be helpful.

Brandon Wood, BSc: Maybe one last suggestion for research would be probably again in the complex API space, but you know, again, when we're going back to, you know, impractical RLDs, it would be really refining what's truly required at the end of shelf life versus what's nice to have, because that in and of itself can reduce the number of samples required at the end of shelf life. That also would be helpful.

Andrew Babiskin, PhD: Bing, yeah.

Bing Li, PhD: Just quick comments about that, you know, gentleman's question. The reason that we recommend PB analysis with three batch is to incorporate the inter-intra batch variability into the consideration. And also, if the industry really have the constraint and the limitation and could not get three batch of the reference product, we also did have case that we stay flexible to allow two batch of reference product in the analysis. That's comment number one. And comment number two is talking about the reference product variability, three batches. Actually, certain certain statistic criteria did widen, you know, the BE criteria if you have more batches or more variabilities in the reference product line that could be reflected in our reference product reference (..) analysis for oral solid drug product, and also in certain cases in PBE analysis. **:** Thank you.

Andrew Babiskin, PhD: ok, I'll try to cue off this next topic. We have limited time. So this is on expanding waivers of in vivo bioequivalent studies. So. The little bit change of gear here, even though this includes all products, but for oral products, what needs to be done? What type of research do we have to have more flexibility in giving those waivers? And other things to consider is how modeling tools can be utilized to address this relevant, the clinical relevance, and what type of waiver opportunities are there currently available, but you find to be too restrictive and you think additional research would be needed to expand those. So open up, we only have a couple minutes left, but I'd love to hear industry's feedback on this.

Myong-Jin Kim, PharmD: I want to start this discussion by using the use of AI. For the preparation of this discussion, I just did a quick AI ChatGPT search of how do we be creative or how do we come up with interesting or alternative, provocative way of conducting business in terms of like, where do we go in terms of a waiver or bio waiver approach? And if you were to do that, it's very interesting what you come up with. And I was sitting there thinking, Oh, this is really nice ideas. So once again, my request to you guys, can you come up with some, like, share with us your ideas of, you know, what your challenges are and some of those aspects that we can consider. You know, we have used a very interesting approach, PBPK, as you know, virtual BE, and the strengths of waiver and all those approaches and excipients and all, if you can kind of think about the risk base

when it comes to therapeutic indications, maybe we don't need to be very strict. So can you comment on those aspects? I'd be very interested to hear.

Brandon Wood, BSc: Yeah, this is Brandon. So I think the opportunities are there, right? To your point, the risk profile is huge. If you can, you know, identify lower risk products where there are highly sensitive in vitro tools available, I think they're ripe for the picking. In terms of, you know, what is some of the barrier to uptake? I think the practical reality at times is risk, right? It's, you know, we're in a position where we can't necessarily afford delays in the overall development program. We can't afford to have delays in submission and approval. So sometimes not having an established pathway or current thinking from the agency on that specific topic in and of itself becomes a barrier to uptake because again, you know, a lot of the generic industry is in the risk aversion business. So I think any research there specifically on lower risk profiled products that already have established highly sensitive in vitro products, if there's any type of publications or positions that can be presented, I'm sure you would see an uptake in that approach from the generic industry.

(Audience Member): So this is for the site transfer products. For the IR, definitely we can go with the resolution profile companies. But for the delayed release product and for the modified release product, generally PSG or the FDA guidance ask for one of the bio study. So if there could be something having more on the in vitro part, like guidelines say to go with the IV-IVC correlation, but it is not clear. So if we can have something more research and guidance on that part, then that could be more helpful for the post-approval changes.

Lei Zhang, PhD: Yeah, I also want to comment on, you know, there's a harmonization going on, support the BE for generics, you know, M13A, B, and C. I think the time is really right. I think through the research does play a big role to support harmonization with other regulatory agencies. So I think it would be a good opportunity for us to discuss what the research opportunity to support like the modify release product and other maybe more complex product under international harmonization utilize those research. Just want to challenge the audience and the industry to see where are the most priority areas we should focus on research in the next year or a few years. Thanks.

Brandon Wood, BSc: Yeah, I would just say, you know, probably a paper-based research recommendation, but I think industry's observation or interpretation is that differences in global requirements are not necessarily, you know, scientific principle differences in understanding, but rather differences in overall conservatism. So you know, one, again, probably paper-based research evaluation is to really, you know, dive into those global differences and identify what are truly scientific, you know, foundational differences, what are versus what are more differences in conservatism and is there an opportunity to align there? So I know, you know, we're not getting policy you know, but having the regulatory

background, I can't help it, but it's, you know, I think more of a paper-based research activity to truly understand and tease out what are scientific principle differences versus what are differences in overall conservatism, and maybe there's an opportunity there.

Lei Zhang, PhD: Thank you. I think through the M13A, it's now finalized and being implemented. We'll see what the results will bring. I totally understand the conservativeness across different agencies, but through ICH, it's really science-based, and those are the technical documents we really try to use the science to back up our recommendation. I think the research is the foundation. Yeah, thanks.

Andrew Babiskin, PhD: We will keep this on time, so we'll close out this session. I want to thank you to the panelists for your participation. We didn't get to touch upon every topic, but we started touching upon a little bit, like the harmonization and even some of the SUPACs. So if anyone for the panel or the audience has additional feedback, they want to give us on specific research ideas, please do so through the public docket, and thanks again. Yep. Now, we'll take a break until 10:45 A.M.