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Quick Pulse

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FDA Considers New Rules for Bioequivalence for Locally-Acting GI Drugs

The FDA's Pharmaceutical Science and Clinical Pharmacology Advisory Committee discussed – without any vote – bioequivalence (BE) methods for locally-acting drugs that treat gastrointestinal (GI) conditions. The panel considered general issues and did not discuss appropriate methodologies for specific drugs.

The FDA asked the panel for advice on the role that (1) biorelevant dissolution and (2) systemic pharmacokinetics (PK) should play in developing BE recommendations for low solubility locally-acting drugs that treat GI conditions.

The advisory committee recommended that PK and dissolution testing, with a panel of dissolution tests in various media, be used as long as dissolution can be measured, perhaps combined with simulations from statistically-based modeling. If dissolution cannot be measured, then clinical trials would be necessary. There was almost no discussion of differences between the diseased gut and a healthy gut. The FDA appears comfortable using healthy volunteers/animals and translating that to diseased people and animals. Thus, a company does not have to prove its generic drug performs the same in a sick patient as in a healthy volunteer, provided PK and dissolution testing meet FDA criteria.

The panel also concluded that PK studies are generally advisable, but if there is no measurable absorption in the GI tract they might not be necessary unless there is a change in the drug formulation that would include an excipient known to be an absorption enhancer.

Background

In 2007, the FDA identified development of bioequivalence methods for locally-acting GI drugs as a critical path opportunity. For locally-acting products, the FDA's Office of Generic Drugs (OGD) has been concerned that its usual *in vivo* bioequivalence studies that compare PK parameters may not be an appropriate surrogate of pharmacological activity. This is because the systemic exposure may not be directly correlated to the local concentration of drug in the GI tract that provides clinical efficacy. The FDA can require comparative clinical trials, but the cost of those trials can be a deterrent to generic companies, so the FDA was seeking advice from the advisory committee on BE methods.

Currently, the FDA recommends that:

- For insoluble binding agents, therapeutic effectiveness is determined by the binding capacity of the active ingredient and the disintegration/dispersion of the active ingredient to provide local availability to the site of action. Thus, the FDA recommends *in vitro* disintegration and binding assays for demonstrating bioequivalence for these agents.

- For immediate-release high solubility drugs that act locally in the GI tract, the FDA has granted biowaivers. Products requesting biowaivers needed to show equivalent dissolution to the reference product in the physiologically relevant pH dissolution media. If the proposed drug product has a different formulation than the reference drug product, additional studies including *in vivo* PK, pharmacodynamics (PD), or clinical studies may be recommended.

At an October 2005 meeting of this same FDA advisory committee, it was difficult to reach a consensus. The panel agreed at that time that, in order to prove BE, *in vitro* dissolution along with PK should be acceptable. However, that may be difficult to do for lower or poorly soluble drugs, and that's why the FDA took the issue to the panel again.

THE FDA PERSPECTIVE

Lawrence Yu PhD, director for science in the FDA's Office of Generic Drugs within the Center for Drug Evaluation and Research (CDER), told the panel that the FDA has good guidance on how to determine bioequivalence of highly soluble drugs, but it is difficult to determine BE for low solubility locally-acting drugs because they are unique, "We recognize that clinical trials are probably too expensive, adding to burdens, but that's the way that we're going because we don't have sufficient evidence (for *in vitro* studies)."

For locally-acting GI drugs, Dr. Yu said performance factors such as dosage form, drug substance, excipients, and physiological factors "will have to be considered…This presents an enormous challenge for the Office of Generic Drugs."

Dr. Yu discussed bioequivalence in general and low solubility locally-acting drugs and offered an update on progress. He defined bioequivalence as the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately-designed study.

When are BE studies needed?

- Development of new drugs – to link clinical trial material to a to-be-marketed product and for changes in formulation, manufacturing process, or dosage forms.
- Approval of generic drugs (ANDAs).
- Post-approval changes.

Approaches to determining BE under current regulations are:

- *In vivo* measurements of active moiety or moieties in biological fluid (PK study).
- *In vivo* PD comparison.
- *In vivo* limited clinical comparison.
- *In vitro* comparison.
- Any other approach deemed appropriate by the FDA.

Dr. Yu said, "The PK study remains the most popular, most common…most preferred method…We use the PK study to demonstrate BE especially for ordinary and systemic drugs." He described locally-acting GI drugs as unique, "For systemic drugs, the side action is downstream, so the concentration in the plasma in the blood controls the safety and efficacy. The same PK ensures the same safety, the same efficacy. But for locally-acting GI drugs, the site of action is upstream…The concentration in the plasma may not totally reflect the concentration – by time and location. The PK equivalence…depends on the drug, drug class, site of action in GI tract."

Performance Factors for Locally-Acting GI Drugs

Issue	Factors
Dosage form	Immediate release, delayed release, modified release, etc.
Drug substance and excipient factors	Solubility, permeability, excipients, etc.
Physiological factors	GI motility, GI pH, etc.

The issue is not highly soluble drugs but poorly absorbed drugs or drugs with low absorption. Dr. Yu said that for immediate-release (IR) formulations of highly soluble drugs BE may be demonstrated by *in vitro* tests covering physiological differences, "When there are similar dissolution profiles, we can scientifically conclude that the two products are BE. So what about a highly soluble different formulation? We may study *in vitro*, *in vivo*, etc., so we have a good idea with respect to highly soluble forms what we should do for BE." For highly-soluble IR drugs:

- If the test and reference list drug products have the same formulations, qualitatively and quantitatively, BE may be demonstrated by *in vitro* dissolution tests covering physiologically relevant pHs.
- If the test and reference list drugs do ***not*** have the same formulations, qualitatively and quantitatively, studies including *in vitro*, *in vivo* PK, PD, or clinical studies may be recommended to demonstrate that any formulation differences between test and reference drug products will not affect the safety and efficacy of the test drug product.

For modified-release dosage forms, Dr. Yu said BE for locally-acting GI drugs currently requires *in vivo* studies with a clinical endpoint while exploring alternative, scientifically sound *in vitro* or *in vivo* approaches.

Are there any examples of an excipient affecting dissolution in the intestinal tract such that it caused a therapeutic failure? Dr. Yu said, "For common excipients, the impact is unlikely, but we don't have solid information that it doesn't impact it at all."

Dr. James Polli, a professor of pharmaceutical science at the University of Maryland, speaking on behalf of the FDA, argued that the *in vitro* approach is better than *in vivo* studies for locally-acting GI drugs, but there is no universal *in vitro* test. The reasons for *in vitro* studies are in assessing IR BE for systemically-acting oral products, "Quite often clinical studies, almost by definition, are not as sensitive. Arguably BE is a very high standard. Clinical studies can fail to be sensitive to formulation differences, including BE situations… Is there universal dissolution media that will solve all our problems? For poorly soluble drugs, the answer is no. For poorly soluble drugs, you might see many, many different official tests…Everyone does things a little differently…I just don't think it is worked out."

The advantages Dr. Polli cited of the *in vitro* approach were:

- Reduce costs.
- More directly assess product performance.
- Offer benefits in terms of ethical considerations.

Dr. Polli said there are differences between BE and safety/ efficacy testing, that BE isn't necessarily the same as safety and efficacy. He cited the example of mesalamine (a drug for ulcerative colitis), saying, "Efficacy and/or tolerability of a test drug and placebo are sometimes 'close'…Despite numerous studies investigating the effect of mesalamine dose on clinical efficacy, it remains unclear whether a dose-response for mesalamine exists…Larger studies have not consistently shown a dose-response for mesalamine above doses of 1.5 g/day."

Repeating the message Dr. Yu had, Dr. Polli emphasized that low solubility immediate-release locally-acting GI drugs are more difficult.

What role should systemic PK play in developing BE recommendations for low solubility locally-acting GI drugs? Dr. Polli said PK studies are the norm, but there is an extrapolation assumption – that if the plasma is the same, the absorption is the same, and thus they are therapeutically equivalent. But plasma alone would not differentiate between a product that performs with no systemic exposure and a product which completely fails to release. He concluded, "One could come up with situations where plasma alone would not be acceptable" due to local excipient effects not captured by the plasma profiles, metabolite issues, etc. However, he added, "As far as being a conservative test in general…PK is more discriminating than a clinical study or a PD study. People make big deals out of a 15% difference in C_{max}, but if there is a poor response curve, are we being conservative? If one excludes a clinical study, PK has a very strong track record…(But) if a drug is not absorbed, I'm not sure PK could easily discriminate between a performing product and a non-performing product."

Biomarkers – e.g., PET studies – are being investigated, but Dr. Polli said they are not really ready for prime time yet. He did say that *in vitro* dissolution can be used as a surrogate for BE in ***some circumstances***. But there is no universal dissolution media – different investigators and laboratories use different approaches and methods. Dr. Polli said, "It is a research area, but there is no magic bullet in solving BE problems."

Robert Lionberger PhD, a chemical engineer in the FDA's Office of Generic Drugs, suggested that when biorelevant dissolution predicts *in vivo* dissolution (as assessed by drug absorption or imaging studies), then it will be ready for regulatory use. He added, "When biorelevant dissolution is used in quality-by-design approaches to design the formulation follow solubility drugs, then it is ready." He said that biorelevance and quality-by-design are linked, "You have to measure the success if the formulation changes and if the design changes." He said the FDA would like the committee members to say what evidence they would like to see to reach that point.

Dr. Lionberger said the FDA uses a very conservative definition of low solubility: When the highest strength does not dissolve in 250 ml of aqueous media at any pH between 1.0 and 7.5. Categories of low solubility drugs include:

- Weak acid (only low solubility at low pH).
- Weak base (only low solubility at high pH).
- Reasonable solubility in *in vivo* fluids.
- Truly poor solubility (solubility limited absorption, reduction in fraction absorbed with dose, novel formulation technologies may be used).

He said locally-acting GI drugs may or may not have significant absorption, many can be detected systemically, and PK studies may be requested for safety. He said the rate of absorption related to local GI concentration and location of drug after release from IR dosage form is governed by GI transit.

BE for locally-acting drugs:

- Systemic action: drug in plasma → BE
- Local action: drug in plasma → side effect

Dr. Lionberger gave examples of two drugs – one approved and one not yet approved:

- For high solubility drugs, *in vitro* dissolution in buffer (pH 1.2, 4.5, 6.8) ensures *in vivo* dissolution and supports biowaivers.
- Low solubility drugs are more challenging (ionization effects, etc.).

Example:

- Drug P (prodrug) and Drug A (active).
- A has site of action in colon.
- A is rapidly absorbed from intestine (can be measured in plasma, extensively metabolized in gut wall).

- A is delivered to the colon as a prodrug (P).
- P is cleaved in the colon to form A (12%-35% of A is absorbed, <5% of P is absorbed).

Dr. Lionberger said, "For both of these, there is measurable absorption; a significant amount of A is absorbed, but a small amount of P is absorbed. The prodrug has limited absorption, but it is detectable. If we look at the solubility of this example, focusing on the prodrug, over the pH range the solubility changes. Low pH – the drug has low solubility, and as you get to pH response of the small intestine, you see actually the colon pH to be highly soluble."

He said an OGD working group has considered potential BE methods, including dissolution, PK study (as a surrogate for local delivery and for safety), and clinical endpoint studies, with a look at possible actions: lab studies of dissolution, simulations of GI transit, drug release absorption, and PK. BE recommendations included dissolution of the prodrug and fed and fasting PK of the prodrug and the active drug. He said, "When we think about potential BE approaches, we can consider PK studies, because the drug can be measured and quantified. But when combined with dissolution media, what approach can we take? We can look at (1) different pH ranges and surfactant concentrations to provide the most sensitive formulation comparison, and (2) biorelevant media, but that may disguise differences in formulation (i.e., particle size). Or we might want to investigate using dissolution media (biorelevant) if testing intestinal fluid to demonstrate whether there is significant *in vivo* solubility for this product."

There was not much difference between tablet and suspension products in clinical endpoints in an unnamed drug Dr. Lionberger used as an example. He said, "Dissolution for this product, regulatory methods (release tests) use non-physiological pH and surfactant. By looking at when the drug is released from the formulation and is available for absorption in the small intestine, it suggests that the drug may be soluble in biorelevant *in vivo* media."

For a particular product, Dr. Lionberger said *in vitro* dissolution plus *in vivo* studies provide demonstration of BE (local delivery) for a low solubility drug. The question is how to generalize this to other products?

To spark discussion, he suggested:

- High aqueous solubility in limited pH range – recommend dissolution in aqueous buffers and PK or other study to confirm *in vivo* release, contingent on site of action.
- Drug only soluble in biorelevant media – recommend dissolution in biorelevant media and PK or other study to confirm *in vivo* release and contingent on site of action.
- Drug not soluble in biorelevant media – investigate mechanism for local availability.

Dr. Lionberger said that the more difficult cases are drugs that don't demonstrate high solubility in buffers, "That is the first step for looking at biorelevant media to first evaluate the solubility of the drug to see if that confirms that there is high solubility, and then convince the FDA and sponsors to move toward a dissolution method – and look at other biorelevant media and the role of PK studies. Other studies that are sensitive to *in vivo* release of the product would be the next step. When the drugs are not soluble at all in biorelevant media, then we have to look in a product-specific way to how that product is getting its bioavailability and look at better mechanisms for understanding that product."

PUBLIC WITNESSES

Akorn. An official argued that if the rate and extent of dissolution are similar in comparative drugs, clinical trials are not necessary.

Dr. Dale Gerding of Loyola University, *who holds patents on ViroPharma's Vancocin (vancomycin) – though he claimed he was not speaking on behalf of ViroPharma.* He described the increase in incidences of *Clostridium difficile* infection (CDI) in the U.S., saying that CDI rates of diarrhea and colitis have continued to increase since 2002. Currently, non-absorbed oral agents that are locally active such as vancomycin and new investigatory drugs are the most effective treatments available for severe CDI. He said that no *in vitro* model has been developed for a *C. difficile*-infected GI tract and the best *in vitro* model to demonstrate bioequivalence in CDI is uncertain, "Given that vancomycin is currently the preferred treatment for severe CDI, we must have some clinical evidence of efficacy for generic agents prior to exposure of patients with life-threatening CDI to formulations that have never been given to humans. I suggest that the FDA openly discuss both the uncertainties inherent in any BE method proposed for CDI as well as the risk and benefits to patients."

A panel member asked how many patients it would take to do a study showing a 25% difference in delivery to the site of action between two drugs. Dr. Gerding responded that it would probably need "a minimum of 100 patients in each group, and even then you'd have to do a power calculation. The FDA requires a delta to show non-inferiority, and you're asking that same question. Those trials are generally running about 200-300 patients right now."

Axcan Pharma. An official told the panel that the release characteristics of mesalamine suppositories are "multifactorial and unique compared to oral drugs." He said that they have low solubility and "non-immediate" release characteristics. Axcan supports the FDA's draft guidance on mesalamine, published in May 2007. He said that *in vitro* and *in vivo* methodologies have not been agreed upon to establish BE in locally-acting rectal suppositories. He concluded by saying that currently available data support BE studies with clinical endpoints and BE studies with PK endpoints on a case-by-case basis.

PANEL DISCUSSION

There was an interesting discussion of the use of healthy volunteers vs. actual patients:

- *Panel member Marilyn Morris PhD, a professor of pharmaceutical sciences at the University of Buffalo*, repeatedly questioned whether transporter action in patients with a GI disease could be differentially affected by different excipients and could be different from the transporter action in the healthy volunteers normally used in BE studies, "PK studies are generally done in healthy individuals, where you are doing comparisons. My concern is that it has been shown that certain transporters, for example in the colon can be affected by disease…In ulcerative colitis transporters can be induced, so there would be differences in tissue uptake and potentially in absorption. Has this been considered?"
- *Dr. Lionberger* responded, "Generally, we get this question a lot on BE studies, even for systemically active products – whether we should do BE studies in patients or healthy subjects…We really think (using healthy subjects) is the appropriate thing to do…If there aren't differences in healthy subjects, you wouldn't see differences in patients with conditions."
- *Dr. Marilyn Morris:* "Generally, that would be true except with the problem of excipients. If excipients can affect transport, then you will come into issues…If excipients are known to affect transport, you may see differences. Otherwise, I wouldn't expect differences."
- *Panel chair, Kenneth Morris PhD, a professor of pharmaceutics at the University of Hawaii*, wondered, "So, unlike systemic absorption, it may be something more sensitive locally than systemically?"
- *Dr. Marilyn Morris:* "True…You should see some compound changes in transport with disease for both products. It is just that if there is an effect on transporter by excipients, that can lead to differences."
- *FDA's Dr. Yu:* "Many academic researchers found excipients may affect transporters…Excipients utilized in *in vitro* are not (necessarily) utilized in tablet and capsule forms. They are sometimes used…I'm not sure the impact of excipients on transporters are real. There is not a lot of evidence on absorption. We are still confident on BE in healthy volunteers."
- *Dr. Marilyn Morris:* "Some of the transporters are upregulated in certain GI diseases, such as inflammatory diseases, and some of these have not been well-characterized...So, I think it is an area that needs to be looked at… and it may be very relevant for some drugs used to treat GI diseases."
- *Arthur Kibbe PhD, chair of pharmaceutical sciences at Wilkes University:* "The transporter issue may be a red herring."

How useful is imaging? Panel member Marvin Meyer PhD, a professor emeritus of pharmaceutical sciences at the University of Tennessee College of Pharmacy, said, "It bothers me a little when some of the methodology like imaging is put down as a solution to some problems, and I would question who is going to do that. The generic folks won't invest the kind of money it takes to correlate *in vivo* and imaging, and the brand name folks might be a little hesitant to prove a simpler way works because then the generics would use it…so is that practical? Dr. Lionberger responded, "Who should pay is a question…We hope to get some of the people who benefit from generics to fund some of the research…I don't know if that will happen…Innovator companies have some interest in better biorelevant media for more efficient product development." Dr. Yu added, "It is highly unlikely that we will use this (PET imaging) as a recommendation for BE studies, just for research."

Panel members also expressed some concern over the use of the term ***biorelevance***. Dr. Meyer said, "I'm bothered a little by the biorelevance term...There used to be a USP test with 10% methanol…I told my students that was biorelevant only for people who are homeless and like to drink aftershave…I'm a little cautious about using the term biorelevant." Dr. Yu said, "This term is not accurately utilized."

Elizabeth Topp PhD, a professor of pharmaceutical chemistry at the University of Kansas, offered an overview on locally-acting drugs and BE: "I want to compare the locally-acting drug issue with the issue of other drugs with other sites of action, such as an oral drug intended to act on a tumor. What I would really like to know is not the plasma concentration as a function of time but the tumor concentration as a function of time – the cumulative exposure of the tumor over time and peak concentration in the tumor, relevant to the issue I'm trying to treat. Generally, I can't know that, so what I have to settle for is a measure of plasma concentration as a function of time. This isn't what we really want to know. CP_{max} is a surrogate for what we really want to know, which is the concentration at the site of action. I would like to apply this same thinking to locally-active GI drugs. What would I really like to know: the drug concentration as a function of time at the site of action. I can't know that for the same reason I can't know it for the tumor. In this case, plasma concentration vs. time is probably not a good surrogate for what I want to know. Because the plasma compartment is essentially a side effect of these locally-acting drugs…We are downstream…What I really would like to know is the CP vs. T in the GI tract. I would even really like to know the CP vs. T and L (longitudinal position down the tract) plasma concentration as a function of time and position in the GI tract…but I can't get that either. So then, what am I willing to settle for, particularly on the question of how to evaluate a generic drug for its activity in the GI tract? How do I evaluate if a generic is equivalent to the innovator?…I think these biorelevant experiments can be particularly important, but there is the question of what we mean by biorelevant. I don't know what the FDA means by biorelevant. I think…suggesting biorelevant dissolution from

a panel of dissolution media, none of which may be perfect… It may be reasonable for the FDA to suggest a panel of dissolution media taken together…So, if a generic product is comparable to the innovator in dissolution profiles across this panel, they can begin to say these products have a high probability of equivalent effects in the local GI environment."

PANEL DISCUSSION OF FDA QUESTIONS

QUESTION #1. What role should biorelevant dissolution play in developing bioequivalence (BE) recommendations for low solubility locally-acting drugs that treat GI conditions?

The panel chair summarized the panel consensus: "Basically, if we start from the premise on both questions that we're starting with, the process itself, dissolution, and normally you would go through absorption and site of action…Systemically, here we're taking away the compartment center, although there still has to be absorption at the site. With that as our backdrop, the consensus I think is biorelevant dissolution in certain cases…but it might well take on a different scope than dissolution as we do it today in the sense that there might be a panel of biorelevant dissolutions and dissolution media, which someone would have to develop or at least adopt in conjunction with external advice...Then, combine this with simulations of one variety or another, including simulations from statistic-based modeling. If you then draw a correlation that was supported by the physical data, and that if we categorize it a little further…that obviously if there is no dissolution, then there's no dissolution. If that's your first constraint, there's no other constraints, so you have to find another way, and that's probably ***clinical***. In other cases when you get dissolution, but with limited or no systemic involvement in dissolution, then we fall back to our panel – our new panel, probably a new division at the FDA – of biorelevant dissolution in media. Finally, if there is systemic absorption, yet still locally acting, then a combination of PK with an advanced or amplified dissolution scenario would be the consensus of the panel."

Panel comments included:

- *Dr. Marilyn Morris:* "Transporters are induced by disease, but certainly we know that there's both influx and efflux possible in tissue, and in the concentrations from the GI tract that are important. And certainly there could be changes in both directions."
- *Dr. Kibbe:* "Whatever has changed in the patient from being a healthy patient to a person with disease to a person with a different transporter – that all acts on that molecule, and so we've got the same number of molecules on the same spot. We're going to get the same result in that patient, even if the transporters are different. We need to keep track of what we're trying to adjudicate, and that is: Are the two products the same? If we can come up with even dissolution studies…then a lot of the data we get (doesn't) need to be too complex. The only value for me for a drug intended to work locally in the GI tract – from taking PK data – is to make sure that (one) isn't promoting absorption more than another. We don't need three different pHs for dissolution. We can go through whatever sequence we want to segment the GI tract, to see where dissolution is happening with each product. I think with dissolution we'll answer most of the questions."
- *Another panel member:* "I work in bladder cancer. We have dealt with some of these issues before from a scientific standpoint…I look at Questions 1 and 2 and say neither one will get us where we want to be. When we do bladder work, we're able to come up with a way to measure in urine what the concentration would be in the tumor. For the GI it's a little more complicated because you have a moving compartment, not one cavity, and your media will change. The content is changing. Microbes are changing. But there are ways. Systemically you can go at it. Neither is right, but in the middle you have models, and if you take a solution rate constant, plug it in, and look at my margin of error, it will not necessarily push you to do *in vivo* studies, but you can set up some modeling tools."
- *Chair:* "The one place where you might have a question is during development, talking about manufacturers…There may be a good rationale for doing that for the human IND as well."
- *Dr. Marilyn Morris:* "The comment with regard to different excipients and inhibition or maybe induction of transporters by different excipients might have an effect, especially transporters that haven't been characterized to the same extent as some of the ABC transporters. But I agree with (another panel member's) comments on modeling and addressing some of these concerns. Doing PK studies will be important with regard to safety and will provide one aspect of characterization, but in many cases you may see significant differences with poorly absorbed drugs, for example, changing from 2% to 4% absorbed, but is that really clinically relevant?"
- *Jerry Collins PhD, associate director for developmental therapeutics in the Division of Cancer Treatment and Diagnosis at the National Cancer Institute:* "If you combine what has been said, we're essentially trying to find a comfort zone of some observations that will mimic what happens *in vivo*, and we have some very good tools. Dissolution has limits, but as an empirical tool it clearly serves a number of purposes…Everyone here is coming at the comfort zone in different ways, but there is support for the idea that we're getting close to what we want but will probably never have it."
- *Anne Robinson PhD, a professor of chemical engineering at the University of Delaware:* "For highly soluble drugs, the measurement of dissolution very well gives an indication of transport because really what we're trying to capture is whether it is dissolution on its own. You can capture the solubility and transport in the site of action, and that is what this question is getting at. For those drugs that are poorly soluble, can we come up with a

method of dissolution that will give us the same information? If that is the case, if we feel that the dissolution alone should represent both, despite the concerns about different sites of action throughout the GI tract, then coming up with good biorelevant solutions is good."

- *Dr. Topp:* "I'm a big fan of simulation, but I know I can make the answers be what I want them to be…any graduate student can tell you, 'I can make the answers you want, boss.' So, I guess one of the questions that I have is if we're going to recommend – or if it were possible to have – biorelevance solutions combined with simulations, then the simulation itself would have to be a standardized kind of thing. The FDA would have to say, 'This is the simulation we're going to do, and you're going to do it like this.' I don't know if this is where we're interested, able, or willing to go…Back in my day when I did simulations, I could get whatever answers you wanted…Transit times are variable between subjects."
- *FDA's Dr. Yu:* "I agree with you that they are quite variable…but when we look at those data we should look from a population perspective – individual data varies quite a lot."
- *Dr. Jessie Au from Ohio State University,(speaking to Dr. Topp):* "I want to respectfully disagree with you because those are two simulations. In this setting you fix boundaries. In the middle you can change something, but you can't change transit time in the middle…We used to design clinical trials with it, so it can be done."
- *Dr. Meyer:* "Focusing on locally-acting drugs…Let's take three cases: One has no systemic availability and no dissolution…and in that case you have to do a clinical (trial). If there's no systemic availability, and you believe whatever drug it is has to be in a solution to have a therapeutic effect, then there is a chance to with a reasonable panel of *in vitro* methods to have a dissolution test that could serve as a reasonable surrogate. And (for) my reasonable panel, you…might have to do four pHs, etc., and two rotation speeds, etc., and you might say that's extreme, but ask a pharma if they want to do a clinical trial or 25 dissolution tests, and you know what they'll pick. If there is systemic available…I think you could probably get away using PK data if there is a different scene. That's probably difficult to achieve, but, again, compared to a 600-patient clinical trial, a 4% AUC, a 2% AUC might still be a reasonable thing to do, and if you have that systemic availability, then you can look at *in vitro* dissolution, and you have something to correlate it with…That's kind of the way I look at it."

QUESTION #2. What role should systemic pharmacokinetics play in developing BE recommendations for low solubility locally-acting drugs that treat GI conditions?

The chair summarized the panel consensus: "It seems to me that our consensus again is very consistent with what was discussed before. If the compound has significant absorption – and that level can be something leading to further discussion – obviously considerations of toxicity would enter into it. Presenting the same amount of material to the site of location in the GI tract would dictate that a PK study would be advisable. If there is not measurable absorption, there is no real logic that would teach us to do a PK study with the exception of a change in formulation that would include something we know or suspected to be a BMN absorption enhancer."

Other panel comments included:

- *Dr. Kibbe:* "For me, PK is really a safety answer. At the back end you say, (are) these two dosage forms giving rise to the same amount of drug getting in systemically, and I think we have to be careful. If you go from 2% to 4%, that's a doubling but that's not significant. Unless there is some clinical reason to think that there is a threshold of 3% that gives you all sorts of toxicity, that's not what you're looking for. You're looking for some dramatic change that will show how much is lost from the site of action that should have been there. When we start talking about modeling…and you take that into account with PK numbers in the model and get a real good understanding of what's at the site or at the biophase over a period of time, I think you're way ahead of the game."
- *Chair:* "That's spot on. We couched what we said in terms of dividing it into safety vs. performance issues, and in terms of safety issues is the reason that in new drug development that the companies do so many BE studies." Dr. Yu said the average is six studies. Then the chair added, "That's low from my experience…but the reason that you do that along the way is that they want to be sure that the formulation changes that are made in fact don't have an effect. So, in that sense, changes in excipients – whether or not excipients are actually aggravating transporters, or changing membrane availability or whatever – should be manifest in the PK, and that's the safety issue, I fully agree. But for performance, as we were discussing, (Dr. Topp) said that since the site of action doesn't depend on being systemically absorbed, then by definition PK studies would be of limited use."
- *Dr. Kibbe:* "Except for the fact that a high absorption would draw down from the site of use and shorten the duration of effect."
- *Chair:* "Right, except for the fact that you can't sink the putt until you get the ball to the hole. Finally, when there is systemic absorption that does correlate to the site of action locally, then that might be of use…Presumably, that would be clinical…It used to be you'd count the number of legs in the air and divide by four. There has to be some assay of response to whatever disease you're treating. That would be clinical."
- *Dr. Meyer:* "The fundamental question to me is: If I do a PK study and have some small values of systemic availability, and I use those numbers, to what extent am I missing the boat? Am I coming up with the wrong

answer? One formulation is better than another gives a lower systemic availability? I don't have the answer to that."

- *Another panel member:* "If it's systemic, do we want to do PK just because we can, or would it be sufficient to spot check some patients to demonstrate that the innovator and the generic product have identical absorption, and we don't care if we have enough data to do full AUC/PK analysis? Do we do complete PK just because we can, or do we say that in this case the complete profile isn't even relevant?"
- *FDA's Dr. Yu:* "I'm not trying to seek advice for polysoluble drugs, so we're not defending what we're going to do. The key issue is you want the dissolution and the PK and simulation, certainly for safety reasons, even hypothetically, for us to, say, get 2% absorbed or 3% absorbed. We look at 2% vs. 4% absorbed. In reality, you don't know what percent gets absorbed because polysoluble drugs don't have…data available. I'm not saying always, but in many cases we have no idea what percentage."
- *Dr. Marilyn Morris:* "What if we're not able to detect a drug, then we only have dissolution data? Where do we go then? Maybe that's the point where we have to consider doing the efficacy study of PD, some PD endpoint study."
- *Dr. Meyer:* "If we assume that one formulation has a 2% release, another 4%, and the other 98% exits in the feces, is it not appropriate to look at that 4% or 2%?"
- *Gary Bueler RPh, director of the FDA's Office of Generic Drugs:* "If we're going to ask for PK, then the 2% and 4% would be an issue for us. If we're looking at very, very small amounts of absorption, and we know that the drug has very, very small amounts, and we're concerned about some small differences, then we could possibly look at it for safety, but if we're looking at measurable amounts where we are applying BE criteria, then we can combine with some dissolution information and make some answer on BE."
- *Chair:* "That speaks to the point of what the consensus was – that if there was no absorption, then why bother. If there is absorption, for the reason of safety and for the reasons that availability might be affected by prior absorption, it would still be prudent to do PK analysis."
- *Dr. Kibbe:* "That's my point, and we've seen cases where windows of absorption higher up in the GI tract and the amount of drug available could change and affect the load of the doses…I think that if the drug has no measurable absorption from the GI tract, dissolution is the thing that we should use and pH profiles."

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