DEVICES PROPOSED FOR A NEW USE WITH AN APPROVED, MARKETED DRUG

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Reported by: Michael Farkas

A P P E A R A N C E S

DR. RACHEL SHERMAN – PRINCIPAL DEPUTY COMMISSIONER
MR. JOHN WEINER - OFFICE OF COMBINATION PRODUCTS
MS. DIANE MALONEY - CENTER FOR BIOLOGICS, EVALUATION, AND RESEARCH
DR. DOUGLAS THROCKMORTON - CENTER FOR DRUG EVALUATION AND RESEARCH
DR. JEFF SHUREN - CENTER FOR DEVICES AND RADIOLOGICAL HEALTH
MS. SIYEON LEE – OFFICE OF CHIEF COUNSEL
DR. KHAUDEJA BANO - INTERNATIONAL SOCIETY FOR PHARMACEUTICAL ENGINEERING
DR. MELODIE DOMURAD - MERIC MEDICAL SYSTEMS, INC
DR. KIRK SEWARD - MERCATOR MEDSYSTEMS
MR. BRAD THOMPSON - COMBINATION PRODUCTS COALITION

C O N T E N T S

P R O C E E D I N G S

DR. SHERMAN: Good morning, everyone. Welcome to FDA's public hearing on Devices Proposed for a New Use with an Approved, Marketed Drug.

My name is Rachel Sherman. I am the Principal Deputy Commissioner at the Food and Drug Administration. I will serve as the presiding officer for this hearing.

Before we begin, I will make a few administrative announcements. Please silence all cell phones or other mobile devices, as the panel has done, as they may interfere with the audio in the room today.

We ask that all attendees sign in at the registration tables outside the meeting room. The restrooms are located in the lobby, past the coffee area to the right, and down the hallway.

The purpose of this hearing is to provide an opportunity for broad public input on a potential approach for devices referencing drugs, or DRDs, that may allow certain device sponsors to seek marketing authorization for devices labeled for

use with a drug that is already approved and on the market when the drug sponsor does not wish to pursue this new use.

FDA will use the information that it obtains during this public meeting as well as the comments that are submitted to the public docket -- and you're going to hear us say that several times because the docket is really very important, and we do study it very carefully -- those submitted by the public -- to help inform FDA's policy development in this area.

I would now like to ask the FDA panel to introduce itself.

MR. WEINER: Hi. I'm John Weiner, the Associate Director for Policy for the Office of Combination Products.

MS. MALONEY: Good morning. I'm Diane Maloney, Associate Director for Policy in the Center for Biologics, Evaluation, and Research.

DR. THROCKMORTON: Good morning. I'm the Deputy Director for Regulatory Programs in the Center for Drug Evaluation and Research.

DR. SHUREN: Good morning. I'm Jeff Shuren. I'm the Director of the Center for Devices and Radiological Health.

MS. LEE: Hi. I'm Siyeon Lee with the Office of the Chief Counsel.

DR. SHERMAN: Thank you. I would also like to identify the FDA press contact, Lauren Smith Dyer, who's here and waving her hand. If any members of the media are here today, please sign in. And if you have any questions or interested in speaking with the FDA about this public meeting, please contact Ms. Smith Dyer.

However, in keeping with the purpose of the public meeting, which is for FDA to listen to comments from the presenters, the panel members and FDA employees will not be available to make statements to the media.

On our agenda today, we have four speakers -- so we have the luxury of time for once -- with scheduled presentation slots. In order to keep to the agenda as closely as possible, I will outline a few ground rules.

First, this meeting is informal. The rules of evidence do not apply. Only FDA panel members will be allowed to question a presenter. No participants may interrupt the presentation of another participant.

And as today's meeting is a listening meeting, the FDA panel will not be able to address questions.

This public meeting is subject to FDA's policy and procedures for electronic media coverage of FDA public administrative proceedings. Representatives of the electronic media may be permitted subject to certain limitations to videotape, film, or otherwise record FDA's public administrative proceedings, including the presentation of the speakers here today.

The meeting will be transcribed and the transcript may be accessed on the FDA website approximately 30 days after the meeting.

Each individual registered to speak has been given a 15-minute time slot on the agenda. Following each presentation, the FDA panel may

also ask clarifying questions. If a speaker ends early or the questions from the panel do not take the full allotted period, we intend to move to the next speaker. This means speakers may find themselves being called up to give their presentations before the time that is listed on the agenda.

We have at least three of the four speakers present.

For those of you who did not register to make a presentation but would like to present your comments at this meeting, you may be able to speak during the open public comment period of the meeting, which is scheduled to begin at approximately 10:45.

Those interested in presenting during the open public comment period at the conclusion of the presentations should sign up at the registration table outside the meeting room by 10:00 a.m. for one of the five-minute speaker slots that will be available.

This meeting is not your last chance to

comment. The docket will be open until January 15th, 2018, and we strongly encourage all interested parties to submit comments to the docket by that date.

Please see the Federal Register notice, which is available as a handout at the registration table if you would like additional details on how to submit comments to the public docket. Once again, to emphasize, the docket is very important to us and we do appreciate the time and effort that go into the comments.

Before we hear from our first speaker, I'd like to provide a few additional instructions for the presenters. We request that each presenter keep to their allotted time so that we are able to keep to the schedule.

When you speak, you will come up to the podium here, and you will see that there is a small light on the table next to the podium which will be green when you begin. It will go to yellow when there is one minute left. And when the presentation time has ended, it will turn red.

So if that happens, I may ask you to conclude your remarks. I apologize in advance if I interrupt any of you, but again, we request that you keep to your allotted time.

Speakers can provide additional comments that go beyond what they cover by submitting comments to the docket.

Thank you and we will now proceed with the presentations. The first speaker is Khaudeja -- and I apologize if I butcher anyone's names -- Bano.

DR. BANO: Good morning, everyone. I'll be addressing Question number 4 from the docket related to post-market safety reporting, specifically focused on challenges related to that topic. Want to specify -- because I'm involved with so many industry forums, I want to specify this is my personal opinion. Anything I'm sharing here does not represent or reflect the opinion of any organization I work with.

The reason I'm standing here and talking to you is I have an interest in post-market safety,

mainly from a combination product perspective, but specifically this adds more complexity to that existing challenge that we see.

So the devices proposed for a new use with an improved or marketed drug are proposed for three reasons. The first one, either to improve or enhance the safety or effectiveness of an already marketed drug in its approved indication.

Second, to expand use with the approved drug for an indication for which the drug is not approved. And thirdly, any additional benefit such as increasing use of comfort or convenience.

In order to achieve these, there is usually either a change in dose, route, or the delivery rate of administration. The reason I reemphasize this is to highlight this will change the safety profile of the drug product.

The requirement or the expectation based on what has been outlined is for the product -- for the market authorization holder to plan to adequately address adverse events, including medical errors, specifically the areas of

identifying, capturing, reporting, and responding appropriately to adverse events associated with the drug to be used per the DRD labeling.

My concern here is how will a device company, an organization that's set up as a device organization prepare themselves to truly identify -- they won't be able to identify whether an adverse event happened or not, but will they be set up to identify what is causing the adverse event?

I have questions around capturing, and I'll address them a little later. Again, reporting, we need further clarification and understanding, and I want to highlight some of the challenges on those topics.

So when it comes to communicating safety information for such a product, there will obviously be device-related safety information. Then there will be drug-related safety information. I do want to specifically draw attention to the places where interaction between the drug and device will occur.

Where and how will that information be captured effectively enough to be communicated with all the caveats to the end product user, whether it's a healthcare professional or a consumer or a patient?

Now, the how. So what is the recommended most appropriate reporting approach specifically when it comes to drug-related events? Is the organization expected to follow the device reporting approach using the 30-day malfunction report, or the drug biologic pathway to report it in 15 days, or I understand it's not truly a combination product as identified right now, but is the expectation for us to follow the drug device combination pathway, or is there a fourth one?

From a challenge to the DRD manufacturers, the question here is who is going to capture the information and how? Is the organization going to create a new or an additional wing to specifically address the pharmacovigilance aspect because drugs do behave differently?

An adverse event is an adverse event. I understand. But if you look at the depth of how an event is identified, it may differ significantly between how a device organization views it versus a drug organization.

Going back to my question of where will this information be captured, is it going to be captured in a single entity system that's used by the device organization, or do we need two different platforms and databases to be able to handle, capture, analyze the information appropriately?

When it comes to reporting, is this information going to be reported to CDRH or for the drug side are we talking about sending it to CDER?

At a very high level, some of the key challenges -- and I know some of these have been talked about at length, there is a significant gap with missing the safety history when it comes to the drug and its behaviors.

When you think about a pharma organization not

pursuing a certain indication or a certain route of administration or a dosage, there are reasons. Maybe it's at an animal study level that there was data that prevented them. It could be safety. It could be efficacy.

We have to make sure -- how do we ensure that this device organization will have a thorough understanding even from an expectedness assessment of an adverse event? Will there be infrastructure and appropriate training in the organization that now has responsibility for an area that's -- that they are naïve to?

The data architecture questions, I understand that the EMDR update that came out has provisions for including up to 20 drug information fields in the MDR form. That's not enough. That doesn't say anything about the drug and its behaviors.

There are processes that are very unique to drugs, the whole causality assessment, relatedness, the attribution. Similarly, devices have their own, you know, definitions, the whole likely to cause, should it recur, we need -- what

is a malfunction.

When you mix a drug with a device, now how do you define your malfunctions? Is that going to change the approach?

Coding is another challenge. Suppose I have an event I'm ready to submit, whether it's to CDRH or to CDER. There is meta coding on one hand and CDRH has their own codes that they assign, specifically patient codes.

How are we going to address the periodic safety reporting? I have a drug manufacturer who has a certain drug profile. They maintain, monitor, and do the appropriate surveillance.

Going back to the initial requirement of reacting, is the device organization going to be prepared enough to react to what they find because of the drug-device interaction but also because of the changed dosage, the changed route of administration?

We want to learn from history to ensure we do not repeat any of the challenges and learn from it. How are we going to address corrections and

removals, any field actions? Is it going to be easy to discern whether it was a drug quality issue that led to certain behaviors or adverse events, a device quality issue, or a drug-device interaction issue?

I know those will be studied. Will studying it to the magnitude that they will be studied suffice to protect public health?

Some of the challenges for the reference drug manufacturers, suppose they get informed about a new adverse event that's reported to the DRD manufacturer. That information, how are they going to handle it? Are they going to -- is it adequate to update labeling based on general pharmacovigilance practices?

Again, how do we draw the line of off-label use or use error? If there was a product that contraindicated, or in their limitations of use, highlighted a certain use and now I have -- or we have -- a device manufacturer that's promoting that use? Granted, both are right, but if you stand in the place of a consumer or a healthcare

professional, it is confusing. Conflicting information may exist at the same time.

How are we going to inform patients and healthcare professionals about what is use error, what is off-label use, and any additional safety information along the way?

From a logistical point of view, if you think about field actions and corrections, people who have lived some of these, even doing it for a single product, a device recall or a drug recall, or a combination product recall, now think about this complexity where you have two entities that are not even talking to each other, trying to pull a recall.

We all have good intentions, but how will we logistically make it happen? Who will own the product risk profile? Is it the drug manufacturer or the DRD manufacturer?

My closing remarks, there is an additional global product profile that has to be maintained. The drug manufacturer owns that profile, but now this introduces an additional challenge. Do they

include this new route of administration or dosage? How do they communicate that globally?

Again, going back to the causality, if you have an adverse event from a post-market safety assessment, who is going to make the call -- who is the decision maker, whether it's a drug causality, device, or the combination effect? I'll tell you. High concentrations of alcohol in a simple on-market product can cause chelation on some of the delivery systems.

I understand those will be studied, but will they be studied adequately for all markets?

Let's say suddenly the drug is being withdrawn for no reason -- I mean, no safety reason. The manufacturer decides to discontinue the drug, marketing of that drug. Then what happens? Where do we leave our patients?

Another challenge is multiple reports. If the drug manufacturer gets notified, they will -- they have an obligation to report and so will the DRD manufacturer.

Now, you end up with potentially duplicate

reports with discrepant information. Hopefully it's the same information, but could have discrepant information. Who bears the burden of analyzing the post-market safety data of this combination?

I leave you with a big caveat, the clinical trials. There will be other speakers talking about it, but clinical trials help formulate my label.

If done right, we can come out with a very robust label, but the question is, who will take that burden on?

End of day, as I stand here as a safety physician, all that matters to me is safety. I'm all for innovation. But safety comes first. Thank you.

DR. SHERMAN: Thank you for your remarks.

Does the panel have any questions?

MR. WEINER: Thank you very much. I just had one question, a kind of combined issue. Regarding the kind of experience with the drug of the device manufacturer and access to information on safety

events, do you have any thoughts for how they might kind of enhance their understanding of the drug product and how they might ensure reports come to them to address for FDA?

DR. BANO: So if I can clarify, you're talking about how there can be effective communication between the drug manufacturer and the device manufacturer?

MR. WEINER: I guess that's a possibility, but the assumption of the DRD paradigm is that the companies don't have relationships.

DR. BANO: Right.

MR. WEINER: You know, how would you try to manage that implication?

DR. BANO: So to me, there will be adequate public information available. There will be literature available. There are -- clinical trial data is available. There will be comprehensive information, especially if it is a well-established drug product.

So you can rely on that plus the scientific know-how of the drug molecule. But will that be

adequate? I can't say that. It depends on the drug safety profile.

Again, even with an established safety profile, my personal preference would be for some level of communication to occur between the two organizations just to make sure that there isn't something that -- it might not be a safety topic, but there isn't something that would help the DRD manufacturer make the right decision.

So there is publicly available information that they can rely on. Literature would be a good source. Thank you.

DR. SHERMAN: Any other questions?

Thank you for your remarks.

DR. BANO: Thank you.

DR. SHERMAN: Our next speaker is Melodie Domurad from Merit Medical Systems.

DR. DOMURAD: Good morning, and thank you for this opportunity to the Agency, the panel, and the many people who helped organize this meeting and given me the opportunity to speak to you today.

I would like to address Question 7, the

challenges that exist at the investigational application stage and how can those challenges be addressed.

Devices that are going to reference drugs as a group will encompass a wide variety of products with a range of experience about the safety and effectiveness of both the drug and the device separately.

In some instances, however, the device may already have been cleared or approved for use without the drug. The drugs, by definition, are going to have been previously approved. And so there will be safety and effectiveness data for them alone, possibly not for that indication but conceivably having been used or published.

In instances where both of the medical products have demonstrated a history of being safe and effective, that knowledge should be taken into account in review of the IDE and PMA submissions.

I think most people would agree that well-designed Phase 3 prospective studies are critical, but they should also be realistic in scope. They

must be completable studies. Studies that cannot be finished, cannot be enrolled, benefit no one - including the patients. Therefore, the IDE process and the subsequent PMA should not be so burdensome that it cannot be viable.

And the drug referencing device response to the size or the quality of that unmet medical need should be taken into account in that review.

I'm going to give you a specific case in point which I think provides an illustration. Hepatocellular carcinoma accounts for nearly all of the primary liver cancer, is the second most frequent cause of cancer-related death worldwide.

The U.S. cancer update provided by a coalition of the American Cancer Society, the Center for Disease Control, the National Cancer Institute, and the North American Association of Central Cancer Registries, published in 2016, dealing with the years 2003 through '12, indicated that while overall deaths from cancer are decreasing for hepatocellular carcinoma, death and incidence rates increased significantly between 2008 and

2012 and these rates are anticipated to continue rising at least through 2020. So we have an unmet need.

Transarterial chemoembolization has been the most common treatment for intermediate stage hepatocellular carcinoma for over 30 years. For those who are not familiar with this treatment, it's a dual action treatment. The concept, because most liver tumors are not resectable and because there is a lack of organs for transplant, a standard treatment for intermediate stage is through a transarterial catheter to deliver one or more chemotherapies mixed with an ethiodized oil, an emulsion, much like a salad dressing, followed or in conjunction with a type of embolic.

This allows the drug to go into the tumor, to be targeted, and then the embolic prevents backflow and also holds that chemotherapy and emulsion in the tumor.

However, there's also venous outflow. So even with this targeted treatment, you do get systemic exposure. This, however, has been a treatment for

over 30 years. The problem is, there is no consensus.

Different drugs and different combinations and different dosages at different treatment intervals with different follow-up imaging for different endpoints have been, if you will call it, a standard.

Transarterial chemoembolization is identified as a standard of care treatment for intermediate stage hepatocellular carcinoma by the American Cancer Society, the American Society of Clinical Oncology, the National Comprehensive Cancer Network, the American Association for the Study of Liver Disease, and the Society of Interventional Radiology, among others.

So the concept of the treatment is well known. It's been used for a long time, and it is recognized as being effective. However, no embolic, that device agent, has ever been FDA approved for the indication of chemoembolization, which means physicians have no on-label way of performing this standard of care.

I present to you an algorithm here for hopefully some illustration. Looking at hepatocellular carcinoma overall, it is particularly complex among cancers. As with virtually all cancers, extent, size, location plays an important role in treatment decision, but virtually no healthy patients develop hepatocellular carcinoma. It is typically the result of 30 to 40 years of insult from toxins, from -- excuse me -- from toxins, from various exposures, and primarily from viral burden load.

Hepatitis C is most common in the U.S., but B is also well seen. So physicians are making their treatment decisions based on not just the stage and extent of the cancer, but also the stage and the extent of the underlying liver disease that led to that cancer, as well as the cirrhosis which is a side effect which affects liver function. So they are also taking into account the existing or remaining liver function. So multifactorial, of course.

Resection, transplantation, and local ablation

are considered potentially curative. However, altogether, those three account for only about 25 percent of hepatocellular carcinomas. At any given time, looking at the entire population of patients with hepatocellular carcinoma, about 50 percent are receiving transarterial chemoembolization as their primary therapy, a procedure for which no product has been FDA approved.

However, when you take into account the fact that those patients who get resection, ablation, and transplantation frequently have recurrences overall about 70 percent of patients who have HCC over the course of their treatment lifetime will receive TACE, which must now be off-label.

Less than two weeks ago I did a search on PubMed , sorry, using the terms chemoembolization and hepatocellular carcinoma, which resulted in 244,000 publications. All right. This is a well-known treatment for a well-known cancer.

However, despite a great deal of data out there, it's difficult to compare outcomes in

studies because of the variability in the embolic devices, the chemotherapy types, combinations, doses, treatment intervals, endpoints, and that doesn't even take into account the patient population with different stages of disease and different amounts of underlying liver disease.

So with no embolic device approved for chemoembolization, physicians just choose amongst the many possibilities that are out there with studies that are not easy, to compare.

So giving you an example of an IDE process, BioSphere Medical, which is now part of Merit Medical, sought to address this unmet need in 2009 with an IDE submission to conduct a Phase 3 study that is of an embolic. But instead of just following the delivery of chemotherapy, can actually load the chemotherapy ionically so when it's delivered it stays within the tumor and you have sustained dilution. So the concept is identical with less venous outflow, so less systemic exposure.

This embolic device had been cleared

previously for use in hypervascular tumors, of which hepatocellular carcinoma is one of them, three years previously. So there is evidence, clinical evidence, safety and efficacy for the device alone.

The same embolic was CE marked two years prior to this IDE for this specific indication, so there is also data existing for delivery of Doxorubicin, potential adverse events, safety and efficacy. And Doxorubicin itself is one of the grandparents of chemotherapy. And there's a lot of safety and effectiveness data out there.

And because of those 244,000 publications, a lot of it is actually for this indication, although it's not approved for this indication.

A pre-IDE package was sent to the Agency in June of 2009 with prompt feedback in 2000 -- August of 2009, and the IDE was submitted in October 2009.

Over the subsequent year, there were three IDE amendments in response to three deficiency letters with five conference calls, a face-to-face

meeting, a multitude of emails and calls, ultimately resulting in an appeal submitted in August 2010 with conditional approval in November 2010 and full approval in February of 2011, so essentially a year's process to review a device which had existing data and for a drug that had existing data and was used substantially, frequently off-label.

So my recommendation is that the IDE review for devices referencing drugs to conduct clinical trials should take into account the extent of existing safety and effectiveness data for products, the degree and impact of the unmet medical need -- in this case, a growing unmet medical need -- and a requirement that the data be reasonable to demonstrate safety and effectiveness.

Prospective, well-designed Phase 3 studies, absolutely important, but they must be feasible to accomplish. And the PMA review should take into account least burdensome provision and a balance of pre and post-market data collection.

The study that resulted from this IDE, by the time it was actually approved to be implemented, the so-called standard of care, which was off-label, that conventional TACE, was no longer the most commonly used method of conducting this treatment method because of data from Europe, from publications.

There was rapid off-label adoption. So by the time the study could be implemented, only 17 percent -- and this is a published study by GABA and colleagues in 2012. A survey was conducted in 2010, right, the year that the conditional approval was received.

And it interviewed Society of Interventional Radiology members who conducted at least 1 to 10 chemoembolizations per year and a variety of medical facilities. And at that time, only 17 percent of physicians were still doing only the conventional method of chemoembolization.

Thank you for your attention.

DR. SHERMAN: Thank you.

Does the panel have any questions? Dr.

Shuren?

DR. SHUREN: You had recommended that there be an application of the least burdensome approach --

DR. DOMURAD: Yes, sir.

DR. SHUREN: -- in the PMA. And of course, those provisions, there's an explicit reference to devices in the law.

Do you believe that that approach should be applied to entire combination of products, not just the device, but the drug component as well?

DR. DOMURAD: I cannot speak to the wide range. I am sure that this panel knows far more. I am familiar only with the types of combination devices that we would do.

I think, honestly, it depends on the amount of information that is available at the time. So if there is a lot known about the elements, I think it should be applied. If the device is entirely new, or if the use of the drug is completely different from anything that's been seen before, that, of course, needs to be taken into account.

But the size of the study, the amount of data,

and the potential for moving some of that data collection, especially longest-term data to the post-market arena, should be considered as a possibility where the elements are relatively well understood.

DR. SHERMAN: Other questions? I have one. You reference -- you spoke about PMAs and IDEs. Do you -- for DRDs, do you think that there might be an occasion where an NDA or an IND would be more appropriate?

DR. DOMURAD: I do not work for a pharma company, so that's difficult for me to say. I think under certain -- again, this is a very wide field. I mean, if you take all of the devices that might be combined with all of the drugs that are out there, we've got a huge spectrum.

Do I think that there are times when the predominant treatment method -- I'm going to take something -- I'm pulling an example, all right, out of -- but if you have a vaccine, for example, that normally comes in a large vial and once you open it you have to throw it away, so an

individual injection syringe, the vaccine here, the biologic is going to be the predominant mode, and the syringe is going to be the device which is combined with it.

I think in an instance like that, clearly an IND or a BLA would be the appropriate. So where the primary effect is coming from or what the balance is, it should probably have an impact.

DR. SHERMAN: Thank you. Any additional questions? Thank you for your remarks?

DR. DOMURAD: Thank you.

DR. SHERMAN: Our next speaker is Kirk Seward from Mercator MedSystems.

DR. SEWARD: Thank you all. I want to thank the esteemed panel for facilitating this public hearing and to congratulate the Agency on working hard to confront an issue that's important both to medicine and to the development of novel therapies that utilize well-known therapeutic agents, particularly those with well-characterized safety profiles.

My name is Kirk Seward. I hold a bachelor's

and master's degree from MIT, and my Ph.D. in mechanical engineering from the University of California at Berkley. I'm the founder and president and chief science and technology officer at Mercator MedSystems.

We're a company that's developing drug delivery devices for local, site-specific drug delivery deep in the body. As a medical device entrepreneur, inventor, and innovator, I'm happy to be here presenting at the meeting.

It's clear from the written proposal and the requests for comment describing devices referencing drugs, or DRDs, that the process is intended to address the need for greater clarity and promote consistent regulatory expectations among sponsors and innovators of medically necessary therapies. The strong efforts by those who have drafted this proposal is obvious.

There are some points that I wish to clarify and respond to in the public comment, and in doing so, I first want to provide some background in the form of a case study example of where the DRD

process would clearly apply. Beyond that, I'd like to comment on how to establish risk profile in determining Class II or Class III DRD applications, on application of the evidence burden as it relates to standards of substantial evidence or reasonable assurance, and then briefly on user confusion and medication error or use error factors and on identification of generic drugs within DRD labeling.

Finally, I'd like to comment on how the DRD proposal relates to CDRH's regulatory science priorities in 2017.

First, to provide a bit of a background in a case study, at Mercator MedSystems, we manufacture the Bullfrog Micro-Infusion Device. The device is introduced into the arterial or venous circulation and advanced to a target site of interest where the balloon is inflated to push a microneedle through the vessel wall.

At that target site, therapeutic or diagnostic agents can be deposited into the tissues outside of the vessel wall.

It's important to note that this device is already 510(k) cleared based on its demonstrated safety, efficacy, and substantial equivalents to devices previously marketed under 510(k) clearance.

The intended use of the device is that in selective areas of peripheral and coronary vessels, it's intended for the infusion of diagnostic and therapeutic agents into the vessel wall or perivascular area or intraluminal, fairly straightforward.

We've been studying the device in clinical trials with a variety of legally marketed agents including the generic corticosteroid Dexamethasone sodium phosphate for injection. It's a well-known and a well-characterized injectable solution.

These trials are either completed or underway. With the delivery of Dexamethasone, we've been studying an anti-inflammatory use of the drug to reduce vascular inflammation after mechanical interventions to open blood vessels -- to open peripheral arteries predominantly.

While localized anti-inflammatory usage is commonly described within the generic labeling, and with a loose interpretation of the Dexamethasone label, the proposed use of the drug falls within the therapeutic intent of the drug and within the dosage range in the labeling, that being localized anti-inflammatory application, when read strictly against the drug label, the usage can be interpreted as falling outside of the indications for the drug since there is no specifically described perivascular route of administration nor indication for vascular anti-inflammation by local administration within the drug labeling.

While we've contacted generic drug manufacturers who make Dexamethasone sodium phosphate for injection, there has been a complete lack of interest from them in making labeling updates or letting us reference their drug master files.

This makes sense from their perspective for a number of reasons. First of all, when taken as a

group, these companies are not interested in adding new labeling claims to their generic drugs because it introduces new liability, which is offset by only a very limited upside since, in many cases, the generic drugs are sold for less than $10 a vial.

And second, no individual general drug maker is likely to step up and change their label because of the reality of immediate substitution where other generic makers could sell into the indication without incurring the liability taken by the pioneer company.

Based on these behaviors from generic drug makers, we're locked into the old drug labeling but trying to innovate the use of the drug and to provide more information to users. It's clear to us that applications like this fall squarely within the intended purview of the DRD proposal.

Turning now to the individual questions solicited within the request for public comment, I'd like to first look at Question 1 about public health, scientific, regulatory, or legal issues

that should be considered.

In addressing the question, I contend that there are specific regulatory issues that should be considered in this approach, namely that DRDs, while described in the request for comments as most likely requiring premarket approval, or PMA applications, should not be inherently classified as Class III devices, or as Class III DRDs.

In the request for comments, a statement was made by the Agency that DRDs would raise different issues of safety and effectiveness since the drug aspect of the DRD would be new, but this merely qualifies DRDs as not likely to be substantially equivalent to legally marketed predicate devices.

And while this is true in most cases, it simply disqualifies DRDs from traditional 510(k) path. But the result of the proposal was different, that the PMA route would inherently be the appropriate device marketing application.

However, I contend that this isn't entirely accurate since PMAs should only apply to Class III products, which are those that support or sustain

human life, those that are of substantial importance in preventing impairment to human health or those that present a potential, unreasonable risk of injury.

In reality, there are a great many drugs that might be referenced by DRDs that have an exceedingly safe profile in humans based on years of use in millions of patients.

Nothing specifically inherent to DRDs should lead to an automatic classification into Class III. Alternatively, the known safety and risk profile of the drug should be considered in determining the classification of the drug or of the DRD such that DRDs are classified by risk.

In this regard, Class III DRDs, or those with high risk, should require general controls in PMA. Class II DRDs with moderate to high risk should require general and special controls and qualify for traditional or De Novo 510(k) pathway.

Meanwhile, in the case of Class 1 DRDs, which likely exist and are low to moderate risk, only general controls should be mandated.

It's extremely important that DRDs are not inherently mandated to traverse the same regulatory pathway as high-risk Class III devices but that they are regulated based on their risk profile which accounts for what is already known about commonly used drugs, for example.

Let us look now at Question 2, the factors in submission considerations being appropriate and what modifications should be proposed.

In commenting on this, we first look at the DRD proposal in which the standard of evidence for demonstrating safety and effectiveness is proposed to be the substantial evidence standard, which is the standard that applies to the new uses of drugs rather than the reasonable assurance of safety and effectiveness, which is the standard applied in the examination of devices.

While it may be viewed that these standards have the same intent, they appear to be implemented differently in regulatory practice.

At a minimum, the quantity of clinical evidence required or mandated by the standards is

not equivalent.

To demonstrate substantial evidence of safety and effectiveness requires two adequate and well-controlled clinical trials with relevant exceptions such as with label expansions.

However, reasonable assurance, as an evidentiary standard, has no such requirement, and can often be demonstrated with real-world evidence or non-randomized trials that compare treatment group to historical controls or performance goals.

Furthermore, the two standards have resulted in distinctly different types of endpoint data that are allowed in order to support regulatory approvals. For example, substantial evidence, the drug standard, requires clinical outcome measures including improvements in feel, function, or survival.

Again, no such requirement has been placed on devices using the reasonable assurance standard. Rather, device approvals often rely on physical or mechanical endpoints that may or may not be surrogates for feel, function, or survival.

As an example, if a device safely restores what would seemingly be normal anatomy, that has often been deemed enough to allow for approval.

To continue on this theme, there may be drugs referenced by devices that have similar intent to devices where the intent of the drug may be to preserve the device outcome. Examples of this are seen with coated pace maker leads or drug-eluting stents, which preserve the device's functionality. Or in the case of drug-coated angioplasty balloons, which preserve the vessel openness or vascular patency created by the device.

Each of these examples has been designated to have a device primary mode of action, therefore the drug coatings have not been held to the device evidence standards or to the drug evidence standards in their approvals.

The evidence standard applied to the drug component in these combination devices should not be unique to combination products that have a device primary mode of action.

For example, in cases where the drug can be

unlinked from the device, to accomplish the same effect while allowing more patient specific or anatomy specific treatments, such as different device sizing or different drug dosing, a patient's medical condition may be more appropriately addressed and the same regulatory standard should apply as if a fixed dose of drug were coated onto a fixed size device.

This is highly relevant since primary approval outcomes for device drug combinations, such as primary arterial patency, have not been linked to drug substantial evidence outcomes of feel, function, or survival, so a double standard should not be applied whether the drug, whether the device and the drug are applied together or separately.

There may be cases, of course, where the drug product -- where the drug provides therapeutic effect independent of other procedural or surgical benefit, in which case drug endpoints may more easily apply, such as the case in which better delivery of a chemotherapeutic agent for head and

neck cancer patients is enabled by a novel device, for example.

Overall, the DRD process is about unlocking innovation by device innovators that are taking older drugs with a long history of safe use and incrementally changing them.

In regulating DRDs, CDRH should have the same flexibility to determine the validity of endpoints and use the reasonable assurance standard. At the very least, products with similar medical intent should be afforded the same standard of evidence, including what type of endpoints are to be demonstrated.

Other factors also require consideration if drug standards of evidence are applied indiscriminately. If the evidence standard of substantial evidence of safety and effectiveness prevails, then does it make sense that other provisions of drug regulations would also apply to DRDs such as breakthrough designation, fast-track approval, priority review, or exclusivity provisions?

With specific reference to exclusivity provisions, assuming an old drug has no patents covering its use as listed in the Orange Book, what would happen if new patents describing novel methods of use of the drug are issued? Would Orange Book references inherently change in response to these new patents?

In response to Question 4, which addresses issues surrounding possible user confusion and medication error, use error, clearly adequate information should be provided in labeling to prevent confusion or errors. And to this end, the same level of detail should be provided as exists within current standard drug labeling.

This should include supplemental information for each relevant section of the drug labeling where different or new information is related to the new use, including indications in usage, contraindications, warnings and precautions, dosage and administration, adverse reactions, and clinical pharmacology.

In response to Question 6, addressing the case

when multiple versions of the drug, including generics, are marketed, identifying the challenges that exist in identifying which generic drug we're referring to, for DRDs that depend on an injectable solution, we're confident that all generics keep to the same formulation solution. As all ANDAs that reference a single NDA call out the generic name of the drug, the DRD sponsor should simply be able to reference the generic name as well.

If there are specific excipients that should be excluded from the DRD labeling, they should be called out in the dosage form and strength section of the drug supplemental label.

Clearly, the development of a DRD policy or guidance shows the forward thinking of the Agency in confronting complex regulatory issues. It should be just as clear that the CDRH regulatory science priorities should be considered with drafting any such policy or guidance.

In particular, the ability to leverage big data for regulatory decision-making, the

leveraging of real-world evidence and employing evidence synthesis across multiple domains in regulatory decision-making, and the development of methods and tools to improve and streamline clinical trial design should all be accounted for during any policymaking process.

In this regard, the appropriate standards of evidence -- in other words, reasonable assurance versus substantial evidence standards -- should incorporate the guidance offered by these priorities.

To summarize, it's my belief, speaking on behalf of Mercator MedSystems, a company clearly affected by DRD guidance, that DRDs can be a valuable tool in advancing medicine without unnecessary or cumbersome regulatory barriers.

Risks should be assessed independently for DRDs and the De Novo 510(k) pathway should be considered with Class II DRDs. Standards of evidence should be appropriate and should allow for reasonable assurance of safety and effectiveness standards to be applied to DRDs.

And finally, CDRH regulatory science priorities should be strongly considered during the development of any DRD policy or guidance.

I thank you for your time.

DR. SHERMAN: Thank you for your comments.

Questions from the panel? Dr. Throckmorton?

DR. THROCKMORTON: Yeah. Can I ask for some clarification on your response to Question 6.

DR. SEWARD: Mm-hmm.

DR. THROCKMORTON: You said for DRDs that depend on an injectable solution, we are confident that generics all keep to the same solution. I don't understand what that's meant to -- because of course we know formulations change fairly frequently.

DR. SEWARD: Sure. ANDAs that reference an NDA, though, are -- oftentimes have exactly the same excipients. While it may be true that excipients change over time or while formulations change over time, the generics, for example, that we use and that we reference, all have exactly the same makeup. And there's four of them available

on the open market.

In cases like that, where the excipients and the formulations are the same, we should be able to reference the generic name with specific -- I'll point to my third bullet here that if there are excipients that should be excluded from the DRD labeling, they should be called out in the dosage forms and strengths.

For example, use this drug so long as it doesn't include this excipient.

DR. THROCKMORTON: Thanks. And actually, that was my second question, was called out by whom? You're saying that it should be in the device label to require a specific generic product?

DR. SEWARD: Right. And I would actually call it the supplemental drug label, exactly. But the labeling that's provided by the device maker, in this case, the supplemental drug labeling, should include if there are caveats to that rule, that there are a number of different formulations of a drug available.

As that number of different formulations

becomes larger than one, then the drug -- then the device maker and the supplemental drug labeling should call out which formulation specifically is being referenced. Or exclude any formulations that are known to cause any safety issues.

MR. WEINER: I just wanted to try to maybe dumb down or kind of summarize or ask you to summarize your position on data needs.

So I guess the question I basically have is if you assume in a fact pattern A, is a drug company doesn't want to play --

DR. SEWARD: Mm-hmm.

MR. WEINER: -- and they're going to need to get a new label and fact pattern B is going to be labeling the device, only on the device side, should the data vary or are you saying the data should be the same regardless? Is this a legal issue or is it a scientific issue?

DR. SEWARD: That's a good question. It's a scientific issue.

The data should be supportive of the application. The data should be sensible and

appropriate. The data should incorporate the known usage of these, in many cases, incredibly well-known drugs, and it shouldn't be taken in a vacuum that one application of a drug, for example, in a tissue one centimeter away from where it's normally used, is a completely novel approach.

To that end, though, it would be the -- it should be the same data whether it's a drug maker or a device maker pursuing a claim of expanding a label for that data, for sure.

DR. SHERMAN: Dr. Throckmorton?

DR. THROCKMORTON: Thank you for your presentation. This is really helpful. And I'm going to ask another sort of fairly technical question about Question 4.

DR. SEWARD: Yes.

DR. THROCKMORTON: And this was about medication, potential confusion because it's, you know, the different products. And you said that the same level of detail should be provided as exists within a current drug label.

I think our interest here was to try to understand when to be concerned. So we had these two products and it was -- as one product, a DRD comes before us, when should we ask for additional testing? When should the potential for confusion raise to a level that it wouldn't be sufficient to just include the labeling information from the approved drug but, in fact, try to understand whether this combination introduced some new concern about potential confusion?

DR. SEWARD: If the combination introduces a new concern about potential confusion, then it should be covered in one of the aspects outlined here, whether it's the indications, how to use the drug, how to use the drug in this device, for example.

And I do want to be clear that the same level of detail should be provided as exists within the current standard of drug labeling, rather than the current drug labeling in the case that the drug label is 50 years old and doesn't meet the current standard.

That being said, most of what could be said about a drug being delivered in a new way for a new reason or at a new dosage, should be able to be covered within these sections of the supplemental labeling. And the supplemental labeling shouldn't exist in a vacuum either.

Supplemental labeling should be augmentative to the current labeling that's with the drug, right? So if the drug, and the vial of drug says don't use it in juvenile diabetic patients, and you don't include that in the supplemental labeling, it doesn't nullify the drug labeling that travels with the drug as well. It's -- it should be augmentative to that drug labeling.

DR. THROCKMORTON: Thanks.

DR. SHERMAN: So if I could pursue that a little further, you would envision the supplemental drug labeling, which would be if you owned and operated by the device company, to include the information specific to that particular use.

DR. SEWARD: Correct.

DR. SHERMAN: And then adverse events would be reported to the Agency and would -- if the safety profile were to change, that would be the responsibility of the device manufacturer.

DR. SEWARD: That's right. And the liability would be incurred to the device manufacturer for that additional labeling.

DR. SHERMAN: And if it were a generic and new generics came on the market, would it again be the device manufacturer's responsibility to update the supplemental --

DR. SEWARD: If there's any changes to those, sure.

DR. SHERMAN: And one last thing. That was actually very helpful. For your example, if you're willing to comment, do you believe that that is -- your primary mode of action is drug or device? If you don't want to comment, it's fine.

DR. SEWARD: We make a very long syringe.

DR. SHERMAN: Okay. Fair enough.

DR. SEWARD: So I don't think that it can be interpreted that it's not the drug effect that

we're going for. But I would point out that it's a -- the drug effect that we're going for is to maintain the device effect of balloon angioplasty, for example.

So it's not like we're trying to cure something by the injection of a drug. We're trying to maintain the patency of a vascular lumen that's been created by angioplasty or atherectomy, which opened it.

DR. SHERMAN: Okay. And would you see yourself as -- I'm sure you've thought about this -- Class III or Class II De Novo?

DR. SEWARD: I would consider this to very likely be Class II De Novo given the fact that it's a 510(k) cleared device, and it's a drug that's being used within its current dosage range for local administration to accomplish anti-inflammation.

So it's very incrementally shifting the use of the drug in that case, given the risk profile of the drug. I would assume that it's Class II.

DR. SHERMAN: Thank you. Any other questions

from --

MS. MALONEY: I just want to make sure I understand. If the drug company did want to play, what would be the end result in terms of the difference? Is the only difference that when they're not playing, the labeling would be in the device product? But the data and the standard of evidence would be the same in either case?

DR. SEWARD: No. I think that the standard of evidence -- for the standard of evidence, we're looking to what the result of the drug use is, right? Again, if we're -- and frankly, what other products the FDA has regulated using that standard of evidence. There's no greater example of that than with drug coated balloons and drug eluting stents where the drug coated balloons went down the device path because they're chemotherapeutic agent, Paclitaxel, coated onto a balloon and they met the reasonable assurance standard, not the substantial evidence standard.

There weren't multiple clinical trials performed with them. They -- you know, they were

very straightforward device studies that led to PMAs for those products.

If that's going to be the precedent that's set for that type of an application, then other applications should be treated the same whether, whether it's a drug device biologic or otherwise.

So the standard of evidence should be taken for the medicine that you're trying to accomplish or the medical therapy that you're trying to accomplish.

The difference -- and we're working with drug companies on more advanced applications that some of you on the panel are aware of because the drug companies have open INDs for example.

And in those cases, the drug company will have, within their labeling, that the drug is indicated for delivery through a catheter like ours. However, in most of those cases, that's a new chemical entity that they're developing, and so it is a different standard of evidence that's going to be applied to that new chemical entity.

DR. SHERMAN: No other questions?

Thank you for your comments.

DR. SEWARD: Thank you so much.

DR. SHERMAN: Our last speaker is Bradley Thompson from the Combination Products Coalition.

MR. THOMPSON: Good morning. I want to thank you for organizing this meeting, this hearing.

I represent a coalition. And so we've been hard at work for the last month or so since the Federal Register Notice came out. And we've done our best to put together comments today, and I'm going to try and accurately represent those orally. But we are going to be filing written comments, which will be much more detailed.

I was very impressed with the presentation so far because they all followed -- many of them followed your questions. If I answer any of your questions, it's going to be a coincidence, all right? I'm not going to follow the structure. I'm providing sort of more high-level observations.

Let me first tell you a little bit about the Coalition and how it operates because I think it's

very relevant to how we approach this question.

So the Coalition by design are those companies that are very passionate about combination products, and it includes drug, device, and biological companies, about 25 all total.

And we've been around for about 14 or 15 years, and we have a committee structure, and we have a working group that is focused on cross-labeling, which is sort of the heart of some of what we're talking about. I recognize not exactly.

And we participated back in 2005 in the meeting that FDA held with DIA, and it was a very good meeting.

Our organizing principle, because we are so diverse, right -- we have device companies and we have drug and biologic companies. And traditionally, those companies have seen these issues from -- through a different lens at least, right?

So we have a very simple organizing principle in how we adopt policy positions, and that is put

the patient first. What is best for the patient, all right?

Now, if it's a safety and effectiveness issue, that's pretty simple because you use science to figure that out, right? But where it's a policy issue like this, it also includes economics. It's an unavoidable aspect of a question like this.

And I think to some extent, my perception of the folks who are struggling with this issue is there's an emotional component to it. And the emotional component is when a good idea walks through the door, you really want to pursue it. Anybody who cares about the patient, really wants to pursue anything that sounds like it's good for the patient.

But the fact is, economics exist precisely to answer the question of how do you allocate scarce resources? That's the definition of economics. And I know that because last weekend my senior in engineering came to me and said I'm struggling in economics, can you tutor me. And we sat down for a while and I had to review it all.

And as I was looking through all the materials, you end up drawing things like performance production frontiers and budget lines and everything. And it's all -- you know, you graph guns and butter. You graph two different things and try and show an optimization of what, from a societal standpoint, you want to accomplish in the allocation of scarce resources.

Well, at the end of the day, that's what we're confronted with here. We have good ideas that are coming in that may not make the cut for where we need to invest our resources. And that's not -- it's economically driven to be sure. That's how -- that's the system that we have for identifying social optimal.

But at the end of the day, it is a tough decision. If you were a venture capitalist, you would see maybe 1000 people come through your door a year. Many of them would have very good ideas and many of them with good ideas you would have to say, sorry, I can't do it. I've got these other things that are, for various reasons, a higher

priority.

Now, when you're sitting there at the Agency and you're hearing about economics, I recognize that that may not be terribly persuasive. But at the end of the day, you guys are a gatekeeper. And I assume that if someone walks into your office and says, you know what, we tried to raise venture capital, we just couldn't do it, can you lower the bar on safety and effectiveness, you'd say no. All right? For good reason, you'd say no.

But it might break your heart because you might look at the idea and say that's a really good idea. I can't understand why it's not getting support.

It's a tough call. And it's tough on everyone. It's tough on the folks who are making the budget decisions. It's tough on the folks in your chair who are seeing the effects of it. All right.

So that's the basic context of my remarks. So I've been authorized to make five points.

Actually, I haven't gotten to any of those five points, so I'm going to do it quickly now.

The first point, cooperation is best. And I assume that's not a controversial statement, but I'll explain to you why I want to make this point, all right?

When the drug and device company are working together, they combine to know the most about the drug and the device and can really sort through the tough safety and effectiveness issues, all right? And they can do it efficiently, all right?

If you were to adopt a program which created a substantial alternative pathway to cooperation, you might end up discouraging cooperation, or at least not encouraging cooperation, okay? And the fact of the matter is cooperation is hard.

I spent a lot of time almost as a marriage counselor with drug and device companies trying to help them work together because it is hard. They have completely different cultures. Drug companies tend to be big, a little bit more bureaucratic, very slow in their thinking. Device

companies are constantly wanting to go fast, fast, fast. There are commercial differences between the two. There are vocabulary differences between the two. Collaboration is hard.

If you create a pathway that basically means that collaboration isn't needed because you create an easy way for them to go around it, you discourage something that is actually very important for companies to do, and you need to be mindful of that, in my opinion.

Collaboration might, in fact, be the best outcome here. And so you might be looking for policy levers to encourage cooperation. I'm not aware of any real policy levers that FDA has that are significant enough if a deal really isn't attractive to make it attractive.

But if it were really important, obviously we could collectively go to Congress and ask Congress to -- they're in the mood to change tax law, right? We could ask for a tax provision.

Let me be clear, I'm not suggesting that we want Congress to mandate cooperation, but if they

want to incentivize it, that would be great.

But the fact of the matter is you guys or we or somebody would need to go in with data and say the market isn't working, right, because you know, if my son is taking the exam -- he took it yesterday. But if he took the exam and there was a question on it, a really good idea wasn't pursued, does that mean the economic system failed, the answer would be, no, it doesn't mean that.

You have to go beyond that to show that there's some reason it actually should have been pursued economically, not just because it's a good idea because there's a whole lot of good ideas that are not being pursued.

All right, the second point. There are a lot of reasons pharmaceutical companies may not want to participate in a collaboration with a device company.

Back in 2005, as I mentioned, you guys held a hearing, and we testified in that, and a good colleague of mine, Danelle Miller, gave a terrific

presentation, and she covered like 20 different reasons. And I'm not going to repeat it all because there's a transcript that's all there, okay?

But just to summarize, there are scientific reasons to not collaborate. There are business reasons not to collaborate.

Within a drug company, you have people who are the world's leading thinkers on that particular molecule. When someone walks in the door and says I've got an idea for a different way to use that molecule, they have a pretty good intuitive sense of what will work and what won't work. It may not be based on a clinical trial. It may not be based on specific evidence. But it will be based on the fact that they've dedicated maybe 10 years of their life studying that molecule.

So when they say no, that's actually a pretty significant thing. And that may never come through to you, all right? And the commercial disagreement may never come through to you. There may be any number of reasons. It might be the

device company wanted more money than the drug company wanted to give them, or vice versa. It could be any number of things. And you won't know that context for why this didn't work.

The third observation I wanted to offer is we're talking about a universe of projects where the drug company has said no. It's possible, as I just said, that in some cases it's because the drug company genuinely feels that it is a risky avenue to go down, that there are public health reasons not to do it.

If you're in that environment, you just need to understand -- I hope this wouldn't be a common occurrence. I hope it would be very rare. But the drug company might actually oppose what you're thinking of doing. And if they oppose it, that opposition, if they're not part of the FDA process, by definition, there's no cooperation, they're not engaged with you and they're not talking to you, and it just sort of, you know, is done, the pharmaceutical company might need to make that opposition known to their -- to the

patients because it's their obligation to know it.

And so you end up debating these things in a public forum because there wasn't a private forum through which they would have been discussed previously. That's a basic conundrum of this route.

Fourth, and this sort of gets more to the heart of the questions that you posed to us, as we've analyzed the proposal, I want to say that the -- all of our members together believe there is a pathway here that you've identified. And that's a big statement. It may not sound like a big statement, but in my mind, it's a big statement because it means that as we've looked at all of the pieces that you're talking about putting together, to us there seems collectively, pharmaceutical, biologics, device companies, that there is an avenue here.

In my opinion, though, just from the tenor of the Federal Register Notice, you may be underestimating just how rare the circumstances would be when all of these pieces would fit

together, and I'll give you a couple of examples.

First, you make it clear, appropriately so, that you require the evidence of safety and effectiveness, and that you plan to respect the pharmaceutical company's ownership of the data that they've supplied to you.

If you truly subtract out that pharmaceutical data and say that the delta with that data removed is what the device company has to prove, that's a very substantial burden. Just look at what pharmaceutical companies pay to develop that data.

When you take that data out of the equation, it's going to be a very rare medical device company that can actually replace what needs to be replaced, prove what needs to be proven over again. And it'll be very important that FDA not sort of in the recesses of its mind accept certain things as proven, which actually are in reliance on the pharmaceutical company's data.

That's a hard thing to do, to unlearn what you feel you've learned, all right, but that is the task. And so then the demand on the device

company -- and again, I go back to the point because there's no cooperation in the economics of it, I assume you wouldn't lower the standard. I hope you wouldn't lower the standard any more than you would if someone came in and said we failed to raise venture capital money, will you lower the bar. You can't lower the bar, all right?

So that's the first point is those data requirements are going to be very substantial.

Second, there is this risk of confusion in the marketplace when the pharmaceutical company and the device company are fundamentally on a different page message-wise about what they think the public health benefits of this use are. And there's a risk of confusion in that regard.

Post-market change management, that's actually an area where we have advocated that there should be a pathway that allows someone to demonstrate that they can actually manage post-market changes without cooperation. We -- as I said, we've been involved in this issue very long. We filed comments suggesting that that is, in fact, the

case. It's difficult to do, but it is, in fact, the case.

And then finally, post-market safety -- I thought Dr. Bano did a terrific presentation at the beginning of this meeting, and I'm not going to try and duplicate that. But what we're focused on is the instance where the adverse information comes first and exclusively to the drug company.

You really have to follow that through to figure out then what happens. The drug company's the only one to receive that. There's no obligation. There's no cooperation between them and the device company to share that adverse information with a drug company.

They have to review it through an appropriate prism, but they aren't involved in the device, so they don't know all the science on the device. So number one, their own decision-making, how do you do that when you're not -- when you can't go over to the device company and say, well, what's the meaning of this or can you explain that or help me understand the science behind this.

And there's no information being shuttled between them. Now, if you say there should be, then really what you're doing is trying to legislate cooperation because that's cooperation, right, so you can't say there should be cooperation. Nor can you say, well, FDA can step in and manage it. We can ask this one -- this question, then turn around and talk to this one. That's cooperation, too, right? And that's -- and that should be off the table.

So to me, the adverse events are difficult, not impossible depending on the circumstances, but very difficult.

The final point -- the fifth point I want to make is really about the avenue. And I thought -- I loved the discussion. I thought Kirk was -- did a very nice job of presenting a very good case study for how this issue comes up.

The fact of the matter is, you do have to worry about fairness, all right? And it's more than fairness. There's a substance to it.

But the fact is, if there's no cooperation

between the drug and the device company, that does not mean by itself that a different pathway should be available that isn't available when there is cooperation. The cooperation isn't the salient point.

And I think some of you were kind of dancing around this issue. If the product has a drug primary mode of action, if it were a combination product, there's a pretty clear set of rules as to how it would be dealt with.

Now, you're saying this isn't a combination product. I get that. But instead, as a DRD, we want to maybe think about the PMA. Well, the fact is if the drug primary mode of action, if the issues are drug-related issues, if it's proving the safety and effectiveness of the drug because they can't use the data from the pharma company, that's a drug submission. That's an NDA.

It's not a 510(k). It's not a PMA. It's an NDA. And as a consequence, I appreciate that there is a distinction between the two, but you need to make sure that you're being consistent and

not, to use a legal term, arbitrary and capricious.

So in summary, we would say, look, I think this is very fruitful discussion. I'm glad we're having this discussion. I think the Agency came up with a creative and intelligent path, and I do think there is a path through the maze that you've identified, but I really think it's for a very select few.

DR. SHERMAN: Thank you for your comments.

Does the panel have questions? Mr. Weiner?

MR. WEINER: Thank you very much. Just one question. Since a major focus here of your presentation was on economic issues, I just want to kind of peel back on that a little bit. So if you're assuming, as you say we should be assuming, of course, that the device company is prepared to put the money forward to generate the data to get approval of new use, what is the economic issue for the drug company?

MR. THOMPSON: By and large, if the device company can do it all, there isn't an economic

issue. That's what I'm saying. There is a path forward.

I think folks when they read your Federal Register Notice are maybe underestimating just how much they have to prove. It's counterintuitive because to a scientist -- the stupidest thing a scientist could ever think of doing is reproving what's been proven. I'm sure to a scientist, that sounds absolutely absurd.

That's what we're talking about, right? Because we're talking about what was proven previously, was done through with data owned by the pharmaceutical company. If you're not using that data, you have to reprove what that data proves.

So if a device company can do that and navigate the other things -- that's what we're saying -- there is a pathway through here.

MR. WEINER: Just a follow-up to that, I think I know the answer, but just to be sure we're on the -- I'm understanding you correctly, is this analysis applicable regardless of whether there's

a generic approved for the drug or not, or is this only prior to ANDA approval being available?

MR. THOMPSON: So I asked an associate of mine to write a summary so I could sound smart of these rules, and she sent it to me this morning at 7:00 a.m. and it was 20 pages long.

I don't have a simple question for you. There are different settings. There are drugs that have been withdrawn. There are generic drugs. There's implications of the 21st Century Cures language. It's a complicated topic. So I don't mean like -- I am skirting it.

I was going to say I don't mean to sound like I'm skirting it, but I am skirting it. Our written comments will address that more intelligently than I could here.

DR. THROCKMORTON: I want to ask an economic question, too. So as I listen to you behind the tone of this is a rare thing, it's going to be challenging, people need to understand that, I also heard at least a little of a concern about an impact on overall product development. I think

we're all interested in, you know, in creating a pathway to foster innovative development I think is one of the specific questions we asked in the FRN.

Put you on the spot and ask you to say where you believe this pathway, if implemented, would take us as far as fostering innovation?

MR. THOMPSON: I think it would help foster innovation. I think it is well-directed at your goal of creating or identifying, I should say, because it's already there. You're not -- there's not -- we're not talking about new law -- identifying a pathway for device companies to get to market without the cooperation of the pharma company, if they have the money to do it. And so I think you've done what you as an agency would need to do, which is identify the pathway, right?

All I'm doing I guess is sort of being clear about expectations. I think the number of companies that will be able to fund that pathway will be extraordinarily small.

DR. THROCKMORTON: And just to follow up a

little bit, we -- the concerns that we had were on both the device side and the drug side as far as development. So one concern that we've heard voiced is that this pathway might negatively influence choices drug companies could make about product development, expanded indications, that kind of thing.

MR. THOMPSON: Who said that? No, I'm not saying that. Let me be clear. I'm not saying that.

If you literally follow the pathway that you identify, it shouldn't affect the drug company at all, neither positively nor negatively, right, because the drug company can go off and keep doing what it's doing and its board can pick the programs that it wants to support. It'll channel its money into those and it'll keep optimizing its own innovation without being inhibited by this program.

So I personally, as I sit here today, maybe one of my members will tell me that I'm missing something, but I personally think drug companies

would be more or less indifferent to this if done well.

Now, where you could go off the rails is if you start taking their data and using it for someone else's benefit, right, because that does -- we talked about free rider problems, the generic free rider and other. That sort of free rider problem is a major economic problem.

So if you -- I don't mean this pejoratively -- but misappropriate data from one innovator to the benefit of the other, that would be a very bad thing. But other than that, I don’t see how it would negatively inhibit the pharmaceutical innovation. I may be fired tomorrow, but …

DR. THROCKMORTON: I hope not. I'm going to ask you about that reliance question. So in the Federal Register Notice, we identified three general sources of information that we thought the device companies might rely on, talked about publicly available -- you know, literature, generalizable knowledge, and potentially the use of withdrawn NDAs.

Any pieces we're missing or do you have any concerns about those pieces as sources of information that device companies could rely on?

MR. THOMPSON: That's what I asked my younger colleague to research and she gave me the 20-page memo. So I respect the question. It's an important question, and I think we plan to address it. I just can't as we stand here now. Sorry.

DR. THROCKMORTON: Last question that I have, I promise. It has to do with the comments you made about it not always being clear why the drug company chose not to cooperate with the device company. And you sort of raised the idea that the drug company might have some authentic concern about the use of the drug in this particular way.

Were you suggesting that the drug company in some way or the other have an opportunity to make that concern clearer as a part of the process that we're laying out so that they would be in some way or the other made aware that this was a development that was being contemplated and they could say, boy, we've got three studies that you

may not know about that show that this causes cancer, whatever.

MR. THOMPSON: No. See, I'm really not encouraging you to draw the drug company into it. Let me clear about that. I'm actually discouraging you from drawing the drug company into it. But I am saying that that's a weakness of the process, right, because what you're describing is resources, time, effort, money, the sort of thing that the pharma company was trying to avoid when it said no to the device company.

So to -- instead of being drawn into it with a device company, to be drawn into it with the FDA isn't fair because you're basically forcing them to become a participant in this process when they don't want to.

But that's the conundrum because they may have knowledge, and some of it may just be, you know, the wisdom of people who have spent 10 years studying this molecule to -- and they understand how it behaves. You're not tapping into that. And if I were FDA, I'd be really nervous about the

drug company not being at the table because I know you guys are terrific at review, but reviewing isn't the same as spending 10 years of your life in a lab tinkering with a drug product and getting to know it. It's just not the same.

DR. THROCKMORTON: And as you pointed out, we wouldn't be able to look under the hood of the drug materials for -- you know, we wouldn't be able to rely on those data. Thanks.

MR. WEINER: This made me think of another question. This probably goes to your 20-page memo and what you're planning to say in writing. I'm not sure.

But on the issue of -- you were saying it wouldn't be appropriate to have a pathway available just because there's a lack of cooperation. Is there an economic issue there, too, or are you expecting sort of backdoors people could get better protection for less cost by using this pathway, or is that not one of the issues you're raising for the drug industry?

MR. THOMPSON: Can you restate it? I'm not

sure I followed what you asked.

MR. WEINER: I may be asking a question that has nothing to do with what you were saying. I had the impression what you were saying was if people have an easier pathway or a more protected pathway, whatever it might be, that should be available regardless of whether you have cooperation or not. Is that what you were driving at and, more particularly, does that mean that you could have --

MR. THOMPSON: Yeah.

MR. WEINER: -- this pathway, and therefore, the paradigm of the NDA pathway wouldn't apply to you and there might be pluses or minuses to that for that company or for their competitors?

MR. THOMPSON: So there's two sides of this horse to fall off on, okay, which is why I don't envy you in trying to ride the horse.

One side of the horse you could fall off on is making this pathway too easy. If you make it too easy, it means that companies may well not -- choose not to cooperate because this is easy

enough we're going to not cooperate, all right?

That would be a bad thing because from a product development standpoint, talk about things you want to incentivize. Cooperation is something I think you want to incentivize. I don't think you want to discourage it, all right?

Now, the other side of the coin you could fall off on is I assume you're not going to have a gate to this thing which says come in and prove to us that the pharmaceutical company, for example, is being unreasonable in their commercial demands and, therefore, you want to go it alone.

You're going to have to just sort of say here's a pathway regardless of economics, regardless of anything else. It's available to all comers if you want to go it alone rather than say you have to prove that you were treated unfairly by a potential partner and that's why you're going -- so it needs to be open to all. And that creates a bit of a conundrum as to what you're truly trying to achieve.

DR. SHERMAN: Any additional questions?

Thank you for your comments.

As I understand it, we have no other speakers, so that is -- was a very informative, not-full morning.

So on behalf of the FDA panel, I would like to thank all speakers for their presentations and all the audience for their attention, whether in person or by webcast.

Discussing the issues for today's meeting, I also, on behalf of the panel, would like to thank the FDA staff that worked to put this meeting together.

We've had a productive partial morning of thoughtful, insightful comments that have provided FDA with a lot of valuable information to consider on this topic.

We want to encourage all our stakeholders once again to submit comments to the docket for this meeting. As a reminder, the docket is open until January 15th, 2018.

Our next steps will be to review all the information provided during this meeting as well

as the information submitted to the docket.

So to all attendees and speakers, have a safe trip home. The meeting is now adjourned.

(Whereupon, at 10:33 a.m., the meeting was adjourned.)

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I, Michael Farkas, the officer before whom the foregoing proceeding was taken, do hereby certify that the proceedings were recorded by me and thereafter reduced to typewriting under my direction; that said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

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