if we are to preserve the progress we have made thus far in combination technology and achieve further improvements.

First, we have conveyed previously we must reaffirm the agency's past interpretation of primary mode of action, which has allowed so many innovative and important combinations to reach market using device jurisdictional standards.

Second, we must refine and preserve the agency's historic inter-center practice of applying flexible approaches to cross-labeling, an issue that arises not just at the end of a premarket review, but also early on in setting jurisdiction and defining pathways for many novel delivery systems.

Third, we need to create new guidances that allow for more creative and flexible approaches to data development for this class of products, with the device authorities clearly and consistently applied for the device and/or the device component parts of these reviews.

And finally, we need better understanding and clarification of those

circumstances where parallel path review may or may not be appropriate.

These four framework issues are, of course, not the only instances that require continued collaboration attention. For example, enhanced communication and transparency, greater predictability of data requirements, and further efforts to reduce the number of review cycles are all important areas for ongoing improvement.

However, our focus today is on a broader framework of challenges, using the premise that if the framework itself is first optimized to foster innovation and to reduce needless data burdens and avoidable delays, secondary product improvements more easily fall into place.

First and foremost among industry challenges in the jurisdictional standard of primary mode of action and reaching consensus with the agency on the appropriate interpretation of this term.

Before discussing this issue, however, a brief comment on the agency's reference to novel

drug delivery systems in this context. The term suggests devices serving to deliver a drug which may inadvertently misdirect primary mode of action analysis and thus inadvertently misdirect jurisdiction.

For example, some of the devices listed in the Federal Register and agency press releases and Web announcements leading up to this meeting, including orthopedic products containing biomaterials, hyperthermia/drug combinations, and drug eluting stents.

In each of these cases, the device component has been determined to provide the primary mode of action with the drug facilitating the device's performance. These are not drug delivery systems for purpose of jurisdictional determinations. For this reason, we suggest not using the term "delivery systems" unless the primary intended use of the device is, in fact, to deliver a drug.

Without this subtle but important clarification, there may be undue and potentially

misleading emphasis on the jurisdictional role of the drug component.

In interpreting primary mode of action, and as we have conveyed on a number of prior occasions, AdvaMed's member companies have come to rely and build their combination business around two fundamental interpretation standards that have now been replaced for more than a decade.

First, the combined product, that is, the product as a whole is analyzed for purposes of determining the primary mode of action.

And second, mode of action is determined based on the primary intended function of the combined product.

The principal theme of the CDRH-CDER inter-center agreement, as you know, provides that products which are primarily structure, physical repair or reconstruction purpose should be regulated as devices.

For the inter-center agreements from our RFD decisions and from informal center assignments over the years, there has emerged a long and varied

list of combination products granted primary device status based on the intended function of the composite product. Among them, human fibroblast derived skin substitutes, bone cements containing antimicrobial agents, spinal fusion products containing biomaterials, dental devices with fluoride, and condoms with contraceptive agents. All of these examples may deliver a drug or a biologic, but that function was not deemed the primary intended function of the combined product for jurisdictional purposes.

FDA's historic interpretations of primary mode of action have served both the agency and industry well. They have fostered innovation, on one hand, and protected and preserved public health on the other, the precise two goals of the Commissioner's new initiative

Innovation has been fostered because of the legal and policy initiatives that are uniquely available under our device premarket review structure, including early collaboration meetings, 100-day meetings, modular reviews, least burdensome

review principles, and humanitarian device exemption initiatives.

From the public health perspective, we have had over a decade of combination assignments to CDRH, and to our knowledge, not a single post-market safety issue has arisen as a result of these assignments.

For these reasons, maximum use of device jurisdiction authority should be encouraged. If Commissioner McClellan is to truly accomplish his initiative in making innovative medical technology sooner and reducing the cost of developing safe and effective medical products while maintaining standards of consumer production since CDRH jurisdiction over a combination has a demonstrated effective review history in these instances where primary mode of action is otherwise unclear.

And companies believe that a device assignment would serve to foster and advance their technologies. Strong deference should be given to this principle.

For the subset of combination products

that, in fact, serve to deliver a drug, for example, new aerosolized insulin systems and lasers to deliver topical anesthetics, there are other jurisdictional principles that have been placed over the years which like the agency's primary mode of action, interpretation will be important to preserve.

For example, the inter-center agreement provides that for drug delivery devices intended for use with marketed drugs and used together as a system, CDRH will have jurisdiction if the device technology predominates. From this jurisdictional interpretation, whole industries and, indeed, whole new standards of care have been born.

Elastomeric infusion pumps, for example, are delivered systems that historically have been granted device review. CDRH jurisdiction and related innovations under our device authorities have allowed this delivery system technology to progress and evolve quickly from hospital to home-based patient use, bringing improved standards of patient care and significant cost savings to our

health economy.

The challenge of cross-labeling. A second and particularly significant challenge for novel drug delivery systems is cross-labeling. Since 1991, when the agency first articulated its framework for combination products, including how labeling must conform for these products, market introduction of novel delivery systems have been aided tremendously by FDA's flexible approach to cross-labeling issues.

For the last decade, cross-labeling/mutual conformance have been defined through the inter-center agreement. From this inter-center agreement important guidance has been provided both to FDA and industry on the issue of cross-labeling, used not simply for final labeling discussions, but also early on and concerning framework/jurisdictional issues for novel devices intended primarily to deliver drugs.

The inter-center cross-labeling standards are fourfold. First, the inter-center standard states there are three essential aspects of

drug labeling requiring mutual conformance: indications, general mode of delivery, drug doses/schedule equivalence.

If device labeling is generally consistent with these key parameters of drug labeling, the essential elements of mutual conformance will be assumed. When there is general mutual conformance, the agreement states that the FDA should do two things. It should grant CDRH jurisdiction for the product, and it generally should waive additional clinical showing of drug effectiveness.

A second standard. The agency has recognized that as delivery system technology evolves, models of delivery and dose schedules for drugs may inevitably be refined. To accommodate these refinements, two of the three key drug parameters in the standard are described with some flexibility.

Specifically, the mode of delivery need only been the same general mode of delivery, and the doses/schedule need only be equivalent.

Also, the term conformance. Using the standard does not convey verbatim replication of or precise equivalence to drug labeling. Device labeling need only be generally consistent with the labeling of the drug intended to be delivered.

Examples of the precedents that have relied on the flexibility of this labeling standards include continuous delivery devices for insulin and fibron sealant mixing and delivery systems.

As a third inter-center cross-labeling principle, even if there are changes to these three critical drug parameters described in the cross-labeling standard, the standard nevertheless affords CDRH further flexibility to consult with CDER and to resolve those issues through device labeling.

And finally, the inter-center agreement on cross-labeling does not purport to address any other secondary aspects of the drug labeling beyond the three stated parameters of indications, mode of administration and dosage. Under this interpretation second drug labeling issues have been available to be addressed through device labeling

and review.

In keeping with the Commissioner's goal of encouraging innovation in this area, we ask that these four historic cross-labeling standards, reaffirmed through agency device reviews over the years, continue as policy practice in this area. Without these flexible policy approaches, significant new challenges will be added to pathway development for this category of products.

A third challenge for novel delivery system relates to data burdens and the need for new guidance that permit more flexible, more predictable, and more consistent approaches to data development. In the novel delivery system context, data challenges can sometimes be very different depending on whether CDRH or another center has received primary jurisdiction for the composite product.

Compounding these challenges is the reality that, in contrast to certain other forms of combination products, delivery system technology often involves two severable components, and review

standards for those components are not always clear or even applied.

If CDRH jurisdiction has been granted for delivery systems, historically it has been because the drug is marketed, has been generally approved, and the device issues thus predominate. In this context two data challenges have emerged.

First, our members believe that there needs to be stronger emphasis on the principle first articulated in our inter-center agreement that whenever possible, delivery systems need not reprove the fundamental efficacy of a drug already approved for the same general mode of administration, dosage, and indication.

In reaffirming this historic standard, our members ask that the agency provide concrete and specific guidance through examples as to how this principle can be more effectively and consistently applied.

As a second challenge our members also feel strongly that any CDER consult process, while important to resolving unsettled drug issues, not be

permitted, directly or indirectly, to set the review standards for the composite product. CDRH product jurisdiction, if it is to be meaningful, necessarily must involve device authorities.

Defining the combined product. In this context we need to make certain that the tried and true drug standards are not applied to combination technologies. These technologies represent breakthrough thinking and application of established drug standards may not in most instances be an appropriate standard for review.

CDRH has a long history of establishing flexible standards because of the nature of the products they regulate. This history gives CDRH a unique experience based on the development of review criteria for those novel products.

In instances where CBER and CDER have granted jurisdiction of novel delivery systems, it is generally the case that both aspects of the product, both the device and the drug that are biologically being delivered, have been deemed investigational.

In this context, industry data challenges are somewhat different. First, for the device combination of delivery system combination, the agency needs to be clear that device authorities, including least burdensome principles, frame the review for the aspect of the product. This component part of the evaluation could occur through separate review and/or consultation process at the sponsor's discretion, but it is important that it be undertaken effectively.

Too many of our members have expressed concern with the agency's internal assessment, published last October, which acknowledged that some reviewers in CDER and CBER lacked fundamental understanding or appreciation of advice premarket review authorities.

The ability to ensure proper device review becomes more important the more complicated the device design, and complexities are increasing reality for delivery system as many new technologies involve software electronics, electromagnetic principles, ultrasound energy, and other

sophisticated forms of device engineering.

As a second more general challenge, our members convey that when CDER and CBER jurisdiction is granted, there is little, if any, incentive at the moment for reviewers in those centers for seeking mechanisms or employing standards and encouraging the development of novel drug delivery systems.

If we are to achieve meaningful premarket improvements in this area, it will be important to develop new guidance specifically addressing delivery system combinations and acknowledging the sentiments expressed at the agency's January 31st press release which launched this initiative.

At the risk of repeating ourselves in that release, the Commissioner described the agency's desire to help make innovative delivery systems available sooner and to reduce needless costs and burdens while ensuring safe and effective medical products.

We believe this initiative represents a

form of least burdensome philosophy now sanctioned expressly under our device laws. New guidance for novel delivery systems should attempt to reflect this standard as appropriate and consistent with the current law.

We believe that separate guidance specifically encouraging and promoting novel delivery system development will give CDER and CBER reviewers one more reason to think creatively and flexibly about data issues and to avoid any temptation for more doctrinnaire data demands.

A fourth and final issue that challenges the framework for premarket review of novel delivery systems is the subject of separate parallel past submissions, and better understanding those circumstances where parallel review may or may not be appropriate.

In the November hearing on combination products, we let the agency know that our member companies see the advantages and disadvantages of separate applications in different ways at different times, depending upon the specific regulatory,

factual, and business circumstances presented by the particular combination.

We believe, however, that these differing views may be fully reconciled by distinguishing required separate filings that may be an option of the sponsor. Several specific recommendations highlight and explain how this distinction would be implemented.

First, in order to avoid redundant reviews and excessive regulation, only one filing should be required in the majority of the cases. Indeed, we believe that as the consultative process continues to be regulated and improved and held accountable, there should be fewer and fewer mandated separate applications.

There are certain selected circumstances, particularly for novel delivery systems, where a company at its option might see a separate filing as useful for regulatory business/marketing reasons. Factors include:

One, where two different companies, for example, a drug company and a device company, are

involved in the manufacturer of a combination drug delivery system.

Two, where delivery system components are expected to have separate distribution and use/reuse patterns.

And, three, where primary jurisdiction for the combination delivery system has been given to the center other than CDRH and the delivery device component is capable of being separately defined and reviewed.

Examples include novel ultrasound infusing catheters, nebulizers, jet injectors, insulin pens, and drug delivery systems that monitor a patient's vital signs. In these circumstances AdvaMed believes that the separate filings are appropriate.

The key to this recommendation, however, is that the option of the dual filings is left up to the sponsor. We believe this theme of flexibility and sponsor discretion is important if we are to encourage the development of novel drug delivery systems in an industry with such a wide array of

corporate and technological interests.

Your next two questions inquire about areas where guidance would be helpful on how the agency can best collaborate with industry and other institutions in the development and encouragement of novel delivery system technology.

Given the commonality of themes presented by these two questions, we have consolidated a response and have several recommendations to provide. We believe the four framework issues just discussed should be reaffirmed in separate or consolidated guidance documents, and those documents should be developed following notice and comment processes required by good guidance practices.

Further agency collaboration with industry on development of these documents also would be beneficial. We also agree with the agency that a drafting process which is as interactive as possible, for example, through stakeholder meetings, would allow for further debate and reiterative refinement of FDA and public views on those

important issues.

As part of the guidance process we also recommend that the agency's initiative and intent to encourage novel delivery systems be fairly stated and specifically supported. In particular, industry would appreciate receiving concrete examples of how the agency process to reduce needless delays and avoidable product developments cost in the premarket process.

We believe suggestions that the agency already has made concerning improvement and review in communications and proceduralizing combination reviews will facilitate the agency's goals, but we request that additional mechanisms for more efficient review processes and further encouragement of flexible review standards be considered as well.

Implementation of this initiative will work best if all aspects of the agency's review chain are trained well on the principles adopted. If the agency is to have all reviewers consistently thinking creatively and flexibly in this area, there must be regular, internal reminders of this goal to

all three centers involved.

Industry would also appreciate ongoing efforts to make combination product include a novel delivery system database as transparent and as informative as possible, consistent with FDA's nondisclosure obligations and the proprietary interests of sponsoring companies.

Data on approved products should convey primary jurisdiction, time frame for reviews, available information on consultative or collaborative processes invoked, the number of review cycles involved, and public summaries for review.

This database should be separate and apart from other databases for approved products to facilitate industry's efficient review of combination precedents.

With those recommendations, AdvaMed thanks the agency for its consideration of our comments. Our members strongly support the agency's ongoing efforts in this area, and we look forward to working closely with you to further reduce

regulatory challenges and to improve premarket processes so as to foster and facilitate innovation of delivery systems and other forms of combination technology.

Thank you.

(Applause.)

DR. JACOBSEN: Thank you, Keith.

And finally, Christine Allison from the Global Regulatory Affairs Group at Eli Lilly is going to discuss the drug industry's perspective on combination products.

MS. ALLISON: Thank you.

First, I'd like to thank FDA for sponsoring this very important workshop. For those of us that have been working on this type of combination products for years, this is exactly what we have been looking for, an opportunity to have an open dialogue with the agency and to discuss about some of the issues and challenges we have been dealing with and struggling with on a daily basis.

I'm also very honored to be invited as a speaker today.

My presentation goals today is first to give you a brief introduction of the type of products that my company has been working with, and also hopefully walk you through some of the regulatory challenges that we have experienced during development and market applications and post-approval, and then touch a little bit on the challenges that we have experienced working with partners, and some global challenges, and then I'll summarize some key points and conclude it with our recommendations to the agency.

Lilly's experience on the combination product is mainly on the drug-device combination. We are currently working on several innovative products, for example, pulmonary inhalation system for systemic delivery of drugs and also other, you know, interesting, innovative products, and those are all at the development stage.

We also have many years of experience working on the pen injectors, which is already in the market, and for those products we have post development and post approval experience. Although

I don't consider pen injectors as an innovative product, however, I believe that some of the post approval experience that we have will be good examples for us to look forward once the innovative product has been approved in the market.

My presentation will also be focused on the CMC issues.

For innovative products, a lot of time the questions surface very early in the development stage, even before we are ready to request for lead center designation. A lot of time we will have a lot of questions, sometimes drug questions or device questions, and we often struggle which center we should go to to ask those type of questions.

So it would be very nice if we have a single focal point so we can just channel those questions to. So we recommend that the Office of Combination Products be the coordinator and facilitator for identifying the appropriate centers for technical consultation prior to lead center designation.

Some of the challenges we have

experienced is also the consistency in lead center designation. We understand that the statutory history does not mandate that the sponsor has to go to the Office of Combination Products to request for designation of lead center.

So sometimes the sponsor can choose to go to individual center instead of go to the Office of Combination Products. So this could result in some similar products, combination products that result in different lead center assignments. It depends on which center the sponsor goes to first.

And often the consultation centers are not defined at the time of lead center assignments. So we suggest that internal procedure be developed to guide each center for routing those requests to the Office of Combination Products for review to ensure the consistency of lead center designation.

And also we recommend that Office of Combination Products also identify those consulting centers at the time of lead center assignments.

Some of the major CMC challenges that we have experienced for innovative drug delivery

systems, because this type of product is very new and is kind of unique, and because a lot of times the agency has no experience with dealing with this type of product, a lot of time the agency will request a commercial system to be used for pivotal studies.

And this creates a lot of technical challenges for us. It means that we have to lock in the CMC development process in a very early stage of development, and this also prevents us to continue to improve the process during the clinical phase and feed it back to our design.

In addition, early resource commitment is required. Sometimes we have to purchase commercial equipment or even build manufacturing sites in the very early stage of development, sometimes even as early as Phase II or III. It depends on what kind of clinical plan that we have.

And so this is a very typical approach. It compares to the normal product development process, and if we have a change that is not avoidable, then we have to make those changes.

The difficulty is to establish successful, satisfactory comparability protocol between pre-commercial and commercial systems to satisfy agency's expectation. So we encourage the agency to consider the role of reaching strategies to allow product process improvements during the development through commercialization, and also clear and documented expectations from the agencies are needed.

And this is not an easy task. We realize this is not an easy task. Therefore, I think frequent dialogue with the agency regarding specific issues is very critical throughout the entire development process.

The traditional pre-IND meetings, or end of Phase II meetings, it is just not sufficient for us. Therefore, we encourage that the agency to be flexible in granting the request for meetings and consultations when dealing with this type of product.

Another major CMC challenge for us in dealing with this type of innovative drug delivery

system is that the drug and device is an integrated system. This is an integrated system. It's got drug components in there and the device components in there, and both components have to work together as a system.

And, therefore, it requires a lot of time, with frequent consultation with multiple FDA centers and sometimes multiple divisions within the same center.

Currently, based on our experience, alignments and communication with multiple centers and divisions has been a challenge, and therefore, we believe that it would be very beneficial if agency's review team can include members from all relevant centers and divisions from the very first sponsor meeting.

Another major challenge that we face is quality systems. The question is which regulations you apply for the drug-device combination. Is it drug cGMP or should we apply the device QSR or both? And which compliance guidance will be used during the preapproval inspection?

It is our opinion that the drug regulations should apply to the drug portions of the products, and the device regulations should apply to the device portions.

And we also believe that clear policy is needed with regard to the FDA inspections for preapproval inspection of the combination products.

And also, we encourage that the investigators to be trained and to perform combination product inspections using the appropriate regulation for each component of the combination.

Another challenge is during the development, is the regulatory reporting. It's unclear what are the requirements for AE and device reporting during the clinical study. Should we follow the 21 CFR 312 or 21 CFR 812?

Especially when it comes to the device expedited reporting requirements for the device portion submitted under the IND in terms of the device malfunction and the inclusion of the device investigation results.

It is our opinion that in principle, reporting requirements for both drugs and devices should be applied as appropriate. We believe that if device malfunction is reportable under the device regulation, it should be also reportable even if submitted under the IND.

We also believe that device investigation results should be included in the report, and this report should be directed to the lead center doing the review.

As far as the reporting time, we have no preference one way or the other as long as it is clear to us what kind of reporting time we need to follow.

Moving on to the challenges during the market applications, the question is always is it a single or dual submission, and if it's dual submission, would dual user fees apply?

And also, what is the format we should use to include those device information in a CTD submission? And what kind of device information needs to be included in drug submissions?

We support the concept of a single premarket review mechanism leading to a single approval of combination products. We understand that there will be exceptions when the DOS submissions may be more appropriate.

In terms of the formats, submission formats, we recommend that standardized formats and also provide guidance for us to include the data, the data requirements for the device information to be included in the CTD submission.

In addition, the phase-appropriate data requirements for the device to be included in the INDs. From our experience, a lot of times we find out it's very beneficial if we prepare the device information in a format that is familiar with the CDRH reviewer. So if we prepare that information, for example, in a 510(k) format, it will be much easier for a CDER reviewer to hand it over to the CDRH reviewer for consultation.

Moving on to some of the post approval challenges, the difficulties we have encountered the most is when we have to deal with device changes,

when this device information is part of the NDA submission, and currently because there is no clear guidance on how to handle this, it's been a challenge for us.

We recommend the use of the CDRH 510(k) decision tree as a guidance. If we go through the 510(k) decision tree and the conclusion is we don't need to have a 510(k)., we suggest this type of change will be communicated to the CDER reviewer through the annual report.

And if we go through the 510(k) decision trees and the 510(k) is required,, then we suggest that this type of change will be communicated to the CDER reviewer through the NDA Supplement B or C.

Again, talk about the post-approval regulatory reporting requirements. There's currently no clear guidance on how to conduct those AE reporting and device reporting for drug-device combination products. Which regulation should we apply? Is it 21 CFR 314 or 21 CFR 803?

The same challenges when we talk about doing the IND stage is for those expedited

reporting, device reporting, do we include the device investigation result in the report?

It is our opinion that, in principle, reporting requirements for both drugs and devices should be applied as appropriate. We believe that if a device malfunction is reportable under the device regulation, it should be reportable as well when it is submitted through the NDA, and we also believe that the device investigation results should be included in the report.

And those reports should be directed to the lead center that has reviewed the submission and approved the products. Again, for the reporting time, we have no preference one way or the other as long as it's one clear reporting time that we have to follow.

Another challenge we have experienced for the post-approval is the cross-labeling of products intended to be used together. An example of some cases is that some of the 510(k) devices approved in the market, cleared in the market can be used for multiple products. When the drug company

wants to include those devices into the drug label, there's no clear guidance how to do this, to reach conforming labeling.

And since there is not a user fee associated with this type of labeling change, therefore, there's no set reviewing times, and in some cases it takes a long time to have this labeling change accomplished. Sometimes when we are waiting for the approval the device that we try to include in there, the model already is obsolete. We know it is very dynamic in the device work. So that means that we have to then restart it again for this whole entire reviewing process to include the new versions of the model.

And sometimes the reviewer may repeatedly review the data set that has already been reviewed by the other center, and in some occasions the reviewer may request additional data beyond what was required by the other centers.

Therefore, we believe that clear guidance is needed on how to obtain mutually conforming labeling. And we suggest that allowing

the 510(k)-cleared device to be included in the drug label is appropriate, and communication of this type of labeling change be made in the annual report.

To touch a little bit on the challenges we have experienced working with partners, very often a device company may work with multiple drug companies with the same device platform. So those device information will be considered proprietary, and when we have to submit an NDA to include this device information, we will not be able to describe those information in detail without reference to a DMF.

And the regulatory challenges come into play when the reviewer wanted to discussion or has questions regarding to those informations. It would be very difficult for the FDA reviewer to discuss those issues with the sponsor due to the confidentialities. And this is the same challenge once the product is in the market and we have changes made in the device portion.

And sometimes the device company may have a different approach, regulatory approach or

interpretation than the drug company, especially in a controversial area, such as we mentioned earlier, some of the GNP requirements or regulatory reporting requirements.

And I believe that those differences can be minimized once the agency has a clear guidance on how to deal with those issues.

Some of the global challenges that we have experienced. A drug device combination product approved under the CDER NDA may require a market authorization for the drugs and a CD marking for the device in EU, and this reports a lot of challenges in terms of submission document preparations, quality system requirements, post-approval changes, regulatory reporting, labeling, and compliance inspections.

And, therefore, it would be very nice if the agency, when dealing with certain policies and guidance, if you can work with your counterparts in the other parts of the world and work toward a direction of having a global harmonization. That would be very nice.

Therefore, in summary, we have identified many challenges throughout the entire product life cycle for innovative device products. We also identify many areas that we need guidance, such as quality system requirements, post approval changes, regulatory reportings, and cross-labeling.

And we believe continued dialogue between sponsors and the agency is critical to ensure successful development and timely review of market applications.

And in conclusion, we would like to recommend that the agency when setting policy and guidance, please consider using Office of Combination Products as a single focal point to handle the issues regarding the combination products, and keep it simple. If we can do it with one process let's not use two processes.

Reduce redundancy, especially in the reviewing process. If one center already reviewed the data, the other center does not need to review it again.

And also when setting guidance and

policy, not only market applications, please consider also post approval requirements and think through the entire product life cycle.

And the last if not the least, please consider global harmonization needs.

Thank you.

(Applause.)

DR. JACOBSEN: Okay. Thank you very much.

That's the end of this session, and I think we're scheduled to have a break now. So if you could all be back at 3:30, we'll get started again with the FDA session.

Thanks.

(Whereupon, the foregoing matter went off the record at 3:17 p.m. and went back on the record at 3:33 p.m.)

DR. JENKINS: We will begin the FDA session. I'm John Jenkins. I'm the Director of the Office of New Drugs in the Center for Drugs. I'm here substituting for Dr. Woodcock, the Center Director, who was not able to be here because of a

conflicting schedule on her calendar.

It's a pleasure to be here, and I think from what I've been hearing in the hallway, this is the session you've been waiting for, which is FDA perspective on all of these issues.

So I'm going to serve as a moderator, and let me introduce our first speaker. Mark Kramer I think you all know.. He's the Director of FDA's new Office of Combination Products.

Mark.

(Applause.)

DR. KRAMER: Thank you, John, and I'd like to thank Dr. Feigal and Dr. Provost for inviting me to be with you here today and talk about what we're doing.

The first thing I have to do is start out by saying that I've been asked to focus on the role of the Office of Combination Products and the kinds of things we're doing. What I wished we had, and this is what I'm going to cover today, is just to give an overview of what is and what is not a combination product; give an overview of how we

regulate combination products at FDA; talk about the role of our office and also some of the current initiatives that we have gotten underway.

I really wish I had a fifth bullet here, which are the answers, the answers to all of the questions that people have been raising today, but as I think you'll hear, we are beginning to work on these issues, and clearly these kinds of sessions really help give us the kind of input that we need in order to anticipate the products that are coming down the line, and there's clearly a lot of new things that I've heard today in terms of products that we have to anticipate.

So the first thing I wanted to do is start out with a question. Are novel drug and biologic delivery systems combination products?

And I think the answer is it depends, and as I'm going to lay out the definition of a combination product, I think we use the term loosely, but really many of the products that we talk about as being combinations might not meet the regulatory definition of a combination product.

However, they may still raise complicated regulatory issues and, therefore, we sort of, you know, are trying to address these types of products at the same time.

This is a regulatory definition of a combination product, and the regulation provides -- this is in 21 CFR Part 3, 3.2 -- there are really four different types of combination products, and the third and the fourth bullets are tied together.

But sort of the quintessential combination product is a product where the product itself comprises two or more regulated components that are physically, chemically, or otherwise combined or mixed as a single entity, and a good example there would be the drug eluting stent that has been discussed much today.

But it has its forbears, things like antimicrobial coated catheters, heparin coated catheters, condoms with spermicide that have been around really for a long time, and those are combination products, too, and we have been effectively regulating those for quite a long time.

The second type of combination is where we have a kit or a co-package that in itself is comprised of separate products, drugs and devices, devices and biologics, or drugs and biologics. Together they create one product which is a combination product because it contains different types of regulated articles.

And the third category is really one of the most complicated for us, and this is where you have separate products, often provided by or manufactured by separate companies that their use together constitutes a combination product. Both products are required to achieve the intended use, indication, or effect, and where upon approval of the proposed product, the labeling of the approved product would need to be changed. And this is the so-called cross-labeling issue that's been raised by a couple of the speakers earlier this afternoon.

In the interest of time I'm going to run through these examples pretty quickly, but they are in your notebook, devices coated, impregnated or otherwise physically combined with a drug or

biologic. I gave some examples of the drug-device combinations. There are also drug-device biologic examples, such as skin substitutes with cellular components, orthopedic implant with growth factors, and there was one of those that was recently approved in the least year.

Prefilled drug or biologic delivery devices are also combination products. Some of the simplest ones that we have are just prefilled syringes, a syringe that is filled with a drug or biologic is a combination product because the syringe is a device and the drug or biologic obviously is regulated separately.

But we also have insulin, epinephrine, interferon injector pens, metered dose inhaler, transdermal patches, again, all examples of combinations.

Drug or biologics that are provided with an applicator or delivery device; drug-biologic combinations. We haven't spoken about that too much today, but radiopharmaceuticals combined with a biologic or monoclonal antibodies combined with a

chemotherapeutic drug, interferon-ribavirin combination for Hepatitis C. These are drug-biologic combinations.

And then again in that last category of combinations, separate products that may constitute a combination: a hyperthermia device used with a chemotherapeutic drug; photodynamic therapy drug and laser light source, and you'll be hearing from Richard Felten about that soon after my talk.

Diagnostic devices that require the administration of a particular drug or biologic, or a drug requiring a specific diagnostic device. These are examples of separate products that used together might constitute a combination.

What are not combination products? Well, combinations of two drugs, two devices, or two biologics. They may raise some of these types of regulatory issues as well, but in order to be a combination product by the regulation, you have to comprise different types of regulated articles: a drug and a device; a drug and a biologic; or a device and a biologic.

Most concomitant use of drugs, devices and biologics is not a combination product, and also general drug or biologic delivery devices, such as an infusion pump that's not intended for use with an individually specified drug or biologic product, they don't meet the definition of a combination product.

And I think those are some of the types of things we're discussing here today that may actually fall in that last bullet and not technically meet the definition of a combination, but may pose some of the very same issues that combination products raise.

These are the various regulatory approaches we have in our armamentarium. Devices generally get approved under the PMA or 510(k) process and are investigated under IDE. Drugs approved via NDA, studied under IND, and biologics under BLA and studied under an IND.

And what somebody once told me at the last talk I gave where I had this same slide was it's like worlds colliding. If anybody remembers

Seinfeld, there was an episode where George felt his worlds were colliding. His girlfriend was getting to know his friends and his work people, and he didn't like that.

And somebody told me once that's what happens with combination products.

(Laughter.)

MR. KRAMER: But when we look at the intersection here, I think it's what makes combinations unique because we have the regulatory flexibility to apply the most appropriate regulation to a combination product by tailoring the approach to taking pieces of drug regulation, pieces of device regulation or biologics as appropriate.

But what we haven't had in the past was a very consistent way of doing that, and that's what we're in the process of doing.

Some of the things that are unique about the way we regulate combination products, first, as you heard earlier, they're assigned to a lead center based on the s-called primary mode of action. As Jonathan pointed out, not defined in the law, not

defined in our regulations, although we are in the process of formulating a regulatory definition for primary mode of action that will be made available for public review and comment, and we feel that's a very important first step in the process of ensuring that these products are appropriately regulated and that we have a good way for determining which center will have lead review responsibility.

Another one of the hallmarks of combination product regulation is that we often, but not always, have consultation or collaboration between the centers. That is a way of applying the best mixture of expertise to insure that one center can supplement its expertise in order to best understand and tackle the review issues associated with that product.

Jonathan asked me to touch on the difference between consultation and collaboration, and I'll try to do it in ten seconds, but consultation is what we generally have. In most of the cases this is where the lead center is ultimately responsible for all decision-making on an

application.

But we also have an approach of collaboration that allows basically the two centers to have equal votes at the table, and both centers would need to reach agreement on the outcome of a submission in order to approve or disapprove the product.

I mentioned earlier that we do have the flexibility to tailor the premarket regulatory authorities, and we have the same flexibility to tailor the post-market regulatory authorities. So we may have a product that might be subject, for example, to elements of the quality system regulation and to elements of CGMPs.

And we have done that, in fact, with drug eluting stents where the drug substance needs to conform to drug GMPs up until the time that it's coated on the stent, and once it's a combination product, then the combination is subject to the quality system regulation.

The other thing is one application versus two, and this is an important issue not only

because it affects, you know, really the whole regulatory landscape of how these products are regulated, but some companies, as AdvaMed pointed out, prefer one application and some prefer two. And sometimes there are business reasons that affect what a company's preference is.

And we're trying to look at tailoring our approach in terms of making it as -- our ultimate goal is to try to have one application whenever we can, but we recognize that there will be instances where two will be most appropriate in order to regulate a product, and there are cases where a company may actually prefer to have two even if we feel they only need one.

There are user fee issues associated with that. I think Christine mentioned that in her presentation, and therefore, there are important ramifications to a decision as to whether to require one or two applications.

The Office of Combination Products was established in December of this year. We have six main roles that are outlined in the statute, and

this was all part of the Medical Device User Fee and Modernization Act.

We have responsibility for assigning combination products based on the primary mode of action to ensure the timely and effective premarket review of combinations, to ensure the consistent and appropriate post market regulation of combination products.

We also have a role with respect to dispute resolution, review and update of guidance agreements and practices relative to the assignment of combination products, and we have to report to Congress on an annual basis on the activities and impact of the Office and provide some prescribed data.

In terms of the assignment of combination products, the statute tells us that we have to promptly assign an agency center with responsibility for jurisdiction of a combination products, and our goals there is to have as efficient an RFD process -- that's the request for designation process -- as possible and to make it as

consistent, transparent and predictable as possible.

Some of the things we're doing I already mentioned. We are developing a definition of primary mode of action, which we think is probably one of the most important steps of this process, but we're also working on guidance on the selection of premarket authorities so that our reviewers understand what tools are available to them in order to regulate a combination, but that we have a framework in order to do it in a consistent and transparent and more predictable way so sponsors will have a better understanding of how their product will be regulated.

Similarly working on guidance for the one application versus two, we're in the process of continuing to make the RFD process as efficient as possible. We just modified 21 CFR Part 3 for some administrative changes to implement MDUFMA and recognize the Office's role here, and we are documenting the various precedents -- I think Jonathan mentioned this earlier -- to make them much more searchable and readily available. So we were

able to have a much better assessment of what we've done in the past with similar products and can help ensure better consistency.

In terms of review of combination products, again, here what does the statute tell us? Ensure the timely and effective premarket review by overseeing the timeliness of and coordinating reviews involving more than one center, and these are the kinds of things that we're doing in that regard.

We do have an SOP on the inter-center consultative collaborative review process, and on my next slide I'll just give a few quick bullets about that.

We're also in the process now since February 14th actually when we modified our SOP in order to allow us to do this, is to monitor the consultative process between the centers, and what we're doing is when the centers initiate a consult request to another center, they copy us on that request. We sort of have a low-tech way that we're doing this right now, but we're in the process of

developing a data base, basically an automated way of doing this so that we'll know in the background every time one of these consults is going on.

And what we do is we take a pretty active approach when they come in to make sure that the request is clear, that the second center, that is, the center that is being asked to help understands what's expected of them, what the time frames are, and then we monitor that process to make sure that the originating center actually got the input that it was expecting and on time.

We also have an effort underway where we're reporting and tracking other combination products, that is, combinations that don't require consultation, but are combinations nevertheless, and these include things like prefilled syringes and transdermal patches which are typically not consulted out to another center, but there's also a lot more sophisticated combinations as well, where the lead center has developed an expertise over the years and doesn't require consultation.

Well, what we have underway now is a

process where every major type of premarket submission in all three centers as of May 1st is categorized as to whether it concerns a combination product or not and if so, what type, and we actually have eight different types of combination products that we're categorizing, and our first annual report to Congress is due on October 26th, and we'll be providing that data.

This first year we won't have very much to report just because of the time we've started. There won't be a lot of combinations that are actually approved by then, just given the statutory time frames, but the data are being collected and we will really have for the first time knowledge of how many combination products we get each year, how many we approve, what types they are, which centers are doing them, and all of that. And up until now we really haven't had that kind of data.

We're also available as a resource to sponsors and review staff for combination products, issues and questions. We're in the process of developing reviewer tools and training.

For example, on the consultation process, by actively monitoring the consults, we're seeing first-hand a lot of the issues that are presented by consulting reviews, and we have some lessons learned beyond what we thought we had already addressed in the SOP, but real-life practical issues that when somebody is actually looking and seeing every one of these, some of the common denominators of problems, and we're going to be disseminating those to review folks.

The SOP, in two words about the consultation process, says that consults count. Consulting reviews need to be given due priority, and it's all part of the agency's work. So if one center asks another for help, the second center needs to do its part in order to make sure that the lead center is able to meet its review goals.

And the consulted centers are expected to be consulted with respect to the time lines for the consulting review, and in turn, held accountable for the timeliness and the quality of their consulting review.

Very quickly on post-market regulation, the law tells us to ensure the consistency and appropriateness here. What we've begun doing where possible is in our RFD letters providing preliminary determinations of what GNPs and adverse event reporting requirements a combination product will be subject to.

We have two active working groups in this area, one on GNPs, one on adverse event reporting, to be able to provide some of the guidance that Christine Allison from Lilly said was badly needed in this area.

Some general considerations. Really my point here is that one size doesn't fit all. I think that point was made this morning. There is no cookie cutter approach. These products, you know, I think we heard this morning that they really run the scope of a wide variety of different products in the kinds of issues that they raise, and therefore, there is not a one size fits all approach.

We've had combinations approved under HDE with as few as 30 or 40 patients, and then we've

had combinations reviewed with much larger randomized controlled trials.

So I think consultation with FDA is very important. I think some of the technologies that were described this morning I personally hadn't heard about before, and I think it's very important, not that that means much, but I think it's important that these dialogues, you know, the dialogue with FDA begin as early as possible so that we can help work with you on what regulatory pathway will be followed.

Just very briefly, collaboration between the device and drug or biologic sponsors I think is very important. That was mentioned earlier, and I have seen first hand that when the collaboration or cooperation exists, the process does work much better.

It is very difficult, as Jonathan pointed out, for a device company without any drug company or biologic company partnership to be able to independently work on changing the label of an approved drug.

And this is going back to the question in the beginning. If my product is not a combination product, will these initiatives still help?

And I hope the answer is yes. It's our intent that they will. I think they present some of the same issues even though a product may not technically be a combination, and I'd encourage you to contact our office. We do have the liaison role that I think that Jonathan mentioned earlier in working with the centers, and I'm hopeful that we'll be there to help make a difference and make the development program easier for your product.

So I think there will probably be a lot of issues that come up in the Q&A section, and you know, if you have issues you'd like me to address afterwards, I'll be happy to stay after the conference and address them at that time, too.

Thanks.

(Applause.)

MR. JENKINS: Thanks, Mark, for that overview of the Combination Products Office.

I think you're doing a great job there, and we're all very fortunate to have you there.

We're going to enter into a series now of some vignettes about the current approach to review of some of the combination products, and we'll start off with one that has been very hot in the news recently, and it sounds like it has been the topic of much discussion already here today, and that's the drug eluting stents.

We're fortunate to have Ashley Boam, who is the Chief of the Interventional Cardiology Branch in CDRH to give us that overview.

Thank you.

DR. BOAM: Thanks, Dr. Jenkins.

I thank Dr. Provost and Dr. Feigal for setting up this workshop today, and I appreciate being asked to speak on this very hot topic, drug eluting stents.

We've heard a lot about it today, and we have a few more little items on this today.

This is kind of a redundant slide at this point. I should have realized talking at four

o'clock you would have known the answer to this question by now, but for those of you who maybe stepped out this morning, this is an example of a drug eluting stent.

This is a diagram of the Cordis' CYPHER Sirolimus-eluting stent which was approved just this last April. As you can see, the stent consists of a bare metal stent platform with a polymeric carrier in which the drug is loaded, and the drug elutes from the polymeric carrier on the surface of the stent.

One of the things we found to be very important when looking at applications for drug eluting stents is that this really is a three component system. There is the stent platform and delivery system which has traditionally fallen to CDRH for review. There is the polymeric carrier in which the drug is loaded. That has also kind of fallen to CDRH review. And then there is the drug substance which has fallen under CDER review.

So today I wanted to talk about some of the review challenges for drug eluting stents kind

of as a real life example that we've been through in the last couple of years. Some of those topics include regulatory jurisdiction, inspectional authority and site readiness, disparity in statutory and regulatory requirements between the two centers involved, then appropriate leveraging of information from other sources, appropriate preclinical and clinical trial design issues, and then a little bit on post market studies and surveillance.

First, as Mark just ably described, combination products fall under Part 3 of 21 CFR. Request for jurisdiction was made for these products pretty early on, and jurisdiction was granted to CDRH as lead center with Center for Drugs' consultation.

But as you can see, there are quite a number of divisions in both centers that are involved in the review of these devices ranging from the Division of Cardiovascular Devices and the Division of Mechanics and Materials Science within CDRH to the Cardiorenal Drug Products Group, the New Drug Chemistry Group, and Pharmaceutical Evaluation

folks from CDER.

Since CDRH does have the lead jurisdiction for these products, the appropriate marketing submission is a PMA, and the appropriate application to investigate these devices is under IDE.

Just to give you a hint as to some of the complexities of these devices, there are quite a number of areas that require expertise from mechanical performance and testing to drug substance and polymeric carrier chemistry, to animal studies, to PK/PD clinical trial design, and not the least of which, manufacturing.

I guess all of this is to really say that it has really been a successful collaboration between the two centers that has really led to the success that we've had in the review of these applications thus far.

One question that has come up earlier today, Christine mentioned this in her talk, was the question of inspectional authority, and for drug eluting stents, as I believe Mark mentioned, the

inspections are conducted by CDRH's lead center, but have involved participation from reviewers from CDER's Office of New Drug Chemistry.

It's important to note that for these devices, as Mark mentioned, the drug regulations have been applied to the drug substance, and then the device QSR regulations to the finished product.

It's also important for companies who are making these devices to have their validations complete prior to inspection. We have worked very interactively with the two centers and with companies to try to get inspections done as quickly as possible, but it's very important to have all of those validations done.

We understand these are very complex products, but if there are subsequent changes and subsequent validations, we may have to go out for a second time, and it's the best use of all of our resources if we go out once and get you taken care of.

There are a number of differences between the different centers, CDRH, CDER and CBER,

when it comes to marketing applications and the statutory authorities. As you can see, for CDRH an IDE is what's filed to start an investigation, whereas in CDER and CBER you have an IND.

And then for a marketing application for these devices it would be a PMA as opposed to an NDA in CDER or a BLA in CBER.

There are also a number of differences in development. I think this has been pointed out today as well. The rate of technology change for devices is much faster than that for drugs. I believe there was an example earlier that devices can become obsolete within six to 12 months, whereas a drug might be on the market for ten, 15, or even 20 years.

There are a number of other differences that are very important in our consideration of these devices, and that relates to the influence of physician technique on the results, on the number of full scale studies that are usually required, and how we regulate products in CDRH according to risk, in which there are three classes versus one class

for new molecular entities in Center for Drugs.

Companies that are investigating these new products often want to know, well, what kind of information do I need and where can I get it. How do I not have to reinvent the wheel?

And whether you have to reinvent the wheel or not really depends on a couple of items here, and it's really in this table. It depends on whether your stent platform is approved or not approved, and it depends on whether your drug substance is approved or, as we say, unstudied.

The easiest scenario in terms of being able to leverage information from other applications is the box marked one where both your stent platform and your drug substance are approved.

The most difficult situation is where both the stent platform and the drug substance are unapproved or unstudied, and that's the box marked four.

As you can see, there are guidance documents for both centers that can help you to put together the right information to get started with

the study for these devices.

So if I have an unstudied or unapproved drug, what type of information do I need that I may not be able to get from somewhere else? For all of these drug eluting stents, we're requiring that sponsors provide the equivalent information that would be required in a Phase I IND for CDER.

It's also important to understand that an analogue of an approved drug is considered to be a new molecular entity by both CDER and CDRH for these products. So Phase I IND information for an analogue to an approved drug would also be required.

There are several categories of safety information that fall under the Phase I IND requirements. That includes chemistry manufacturing controls, otherwise known as CMC. Both preclinical pharm-tox and systemic clinical exposure in normals are required prior to doing human investigations of the finished product as a device.

It's also important to note that if your drug substances has not been studied before, this Phase I IND safety information could very well

inform on the clinical trial design that would be necessary for the finished product. If there are toxicity issues or potential drug-drug interactions, that are identified during the Phase I safety information gathering. It may be necessary to alter your clinical study to look for those when evaluating the drug eluting stent.

In terms of preclinical testing, I think one of the most important messages we try to get out is that characterization of the finished sterilized product as it is to be studied is really essential. We realize that a lot of changes and design improvements go on during the design and development, product development process, but by the time you're ready to do a clinical trial we really need you to characterize the actual device you want to study so that we know when you get clinical trial results what they really represent.

And a couple of those areas include characterization of the coating and the drug substance, in vitro and in vivo elution characteristics with release rate of the drug, and

also methods and some initial specifications for stability of both the drug substance and the polymeric carrier, if applicable.

Also, adequate animal studies are really needed to assess safety prior to going into human clinical trials for these devices.

A few more specifics here in the preclinical area. Some of the common deficiencies that we see are inadequate stent platform testing in terms of looking at fatigue and corrosion testing. This is not testing that can be leveraged simply from the bare stent platform. With the addition of a coating, it becomes important to look for fatigue and the effects of corrosion through potential cracks in the coating.

We also see inadequate analysis of any surface modifications made to the device, either through application of the coating with the drug substance in it, and so this relates to coating integrity, durability testing, and also characterization of both drug content and its uniformity along the length of the stent.

We also see incomplete in vitro pharmacokinetics both in terms of methodology, and we strongly recommend that sponsors attempt to develop an in vitro/in vivo correlation if at all possible.

This becomes very important in terms of scale up from a clinical trial batch or precommercialization to commercialization manufacturing. It also becomes very important if there are changes or improvements that you want to make in the device because the better you can characterize the device you study, the better you can evaluate what those changes might look like in terms of clinical sequelae.

And also CMC issues not being adequately addressed, stability and shelf life are very important. I think device companies are very much used to a device paradigm where accelerated aging with real time aging to confirm those results have been accepted.

We typically review protocols, and when we're very comfortable with device materials and

device packaging materials, they're pretty straightforward protocols, but when you introduce the drug substance and a polymeric substance, there are a lot of new issues that need to be looked at in terms of stability, and we recommend that sponsors follow the ICH guidelines for evaluation of stability especially of the drug substance.

In terms of animal studies that we receive, we often receive inadequate reports to allow us to make an assessment of safety, to know whether it's appropriate to start a clinical trial, and that involves lack of an evaluation of the doses that are intended for use in the clinical study, and we also require doses higher than this. We require overdosage to make sure that we understand what the toxicity limits are in an animal model.

We look for serial sections of myocardium, arterial histopath, and necropsy reports for any deaths that might have occurred during the study.

As we move to the clinical evaluation of drug eluting stents, first and foremost, we're

looking for a reasonable assurance of safety and effectiveness, and it's important to remember that your clinical trial design should look to meet both of these objectives.

The usual standard of evidence for these products at this point is the randomized controlled clinical trial, and in terms of study endpoints for coronary drug eluting stents, we're looking for primary endpoint or endpoints that include at least a clinically meaningful endpoint.

We're also evaluating the use of surrogate or co-primary endpoints at this point. As I believe Dr. Kuntz mentioned this morning, now that we have an approved drug eluting stent on the market, there are a lot of questions about how do you design a study to be performed in the U.S. if I don't feel I can do a placebo trial because the penetrance has been so remarkable.

And these are some of the areas that we're looking at in working with sponsors as well as our statistics group to come up with reasonable clinical trial designs that will still give us

evidence of both effectiveness, but also, and most importantly, of safety.

We also recommend the use of independent core labs, clinical event committees, and an on-line, very active data safety monitoring board.

I wanted to mention that TPLC is really critical for drug eluting stents. The first drug eluting stent is estimated to have been implanted in over 50,000 patients since it was approved in late April, which is a pretty remarkable roll-out for a new product.

And compare that 50,000 number to the 1,100 patients that we saw in the U.S. clinical trial. There's a lot of information you can get from 1,100, but it's never going to tell you everything about what happens when it gets to 50,000 or 100,000 patients.

And so we feel that information gathered in the post market is very important for these products. We are requiring five-year follow-up for all of the cohorts that have been enrolled in support of an application.

We're also requiring additional data collection in the post market period to get a further understanding of what happens when real docs put these in real patients because we know that sometimes there are differences between what happens in a clinical trial and what happens in the real world.

It's important to note though that in the post market as folks are looking at new indications and new patient populations for these products, those indications and those patient populations should be studied under the IDE process.

There was a question about adverse events earlier, and for these particular products, in collaboration with our folks in the Office of Surveillance and Biometrics and the people in the Office of Drug Safety over in CDER, we have made a determination that for coronary drug eluting stents reports will come to CDRH through the MDR process, but we have made arrangements for data to be shared with CDER, both preapproval and post approval, as information is gained on both sides about drug

substances.

And so in closing, if you have questions, certainly we encourage very early meetings with us. We're happy to meet with you. We're happy to talk with you very early in your process and then as needed again as you get further through your product development.

I'm the Branch Chief that handles the coronary drug eluting stent program. Lisa Harvey is handling the peripheral drug eluting stent program, which I didn't really speak about today, but it has its own set of challenges as you get great big stents with lots more drug and an area where bare stenting doesn't have approved products. So a lot of their own challenges in that group.

But I encourage you to contact the folks on this slide if you have questions, and we look forward to continuing our collaboration with CDER and with the Office of Combination Products to make efficient and effective review of these applications.

Thank you.

(Applause.)

MR. JENKINS: Thanks, Ashley.

We're going to move along quickly. We're running a little long on time. I recognize that, but I see a lot of attention in the audience. So I think that's okay.

Next we're going to talk about photodynamic therapy systems. We have Richard Felten from the General Surgery Devices Branch of CDRH.

Richard.

MR. FELTEN: I'll just actually go to the next slide very quickly.

This I think, hopefully, is a success story, but it also gives a good idea of how we got where we are in this particular area. If you'll notice from the slide, there is a pre-1984 date. The drug that initiated photodynamic therapy and the combination product review that we used to get this finally to market was originally submitted as an IND in 1978.

We became involved from the standpoint

of devices with this product in early 1980, '81, by being asked by the Center for Drugs to look at the light source that was being used to activate that drug.

We formalized that arrangement in 1985, where I was actually designated as the lead reviewer from the Center for Devices to look at these products at the time..

In 1989, we developed a collaborative process for review with the Center for Drugs following lots of conversations between Center for Drugs, Center for Devices, and the company on how best to proceed with these products, and as formalized through the interagency agreement in 1981.

The reason we did this is -- and you've already seen this slide sort of -- Center for Devices has a very involved process in getting things to market. You have premarket notification, PMAs, the premarket notification that's in our 510(k), the premarket approval which is PMAs, and some other sources, where essentially drugs has NDA.

The generic drug approval process is not even close to something we do.

The problem, therefore, was how to take these products and have them reviewed efficiently and at the same time make sure that both the device and the drug were being addressed in the appropriate ways.

The important thing to remember in this area is all of these drugs are brand new drugs. These are not already marketed products. These do not have a history. These are brand new drugs.

In some cases they are derivatives of biological products like human blood. Other times they are simply chemistries that somebody has developed on a lab bench that has a photosensitive property. So that alone is what led us to decide that Center for Drugs would have lead in all of these products with Center for Devices acting as the consultant.

The way this worked was we encouraged the companies through conversations to have these meetings with us. Center for Devices took lead. We

consulted the Center for Devices on the device section. All official correspondence during the initial IND stage was sent through Center for Drugs to the drug company. The device companies were involved peripherally through the drug company to submit their device section as part of the IND. We reviewed the device section, sent our comments to Center for Drugs, who reported back to the drug company, who talked to the device company.

As Jonathan has mentioned, although nobody believed it was going to work, it apparently worked very well and very efficiently. We did have an oral arrangement with Center for Drugs that allowed me to talk directly to device companies if I needed to, but official correspondence was always through Center for Drugs.

Once the clinical trials were completed, the issue came up then how do we submit this application and what do we do with it. One of the interesting parts of this particular initial application which was for a drug eventually called Photofrin was that the drug company very clearly

told the agency, "We do not want to be a device company. We want to have nothing to do with the devices once you approve this."

And the reason for that was that in the initial first one of these drugs, which was Photofrin, the light source were commercially available surgical lasers. Surgical lasers, as laser products, have regulatory responsibilities under the Center for Devices' performance standard for light emitting products. The drug company didn't want to be a device manufacturer because they didn't want to be responsible for all of the reporting requirements lasers have once you market them and post market.

In those conversations with the drug company, who very clearly said, "We don't want to be a device manufacturer," between Center for Drugs and Center for Devices there was an agreement reached that what would happen would be that a single application would be submitted as an NDA.

We, the Center for Devices would take the device section out of the NDA and convert those

into PMAs. We made three PMAs out of the device section, two laser PMAs and a fiber optic PMA.

Now, the reason we did that was, of course, to make this work more efficiently for the drug company after the approval process because once they sold off the device sections, we needed a way to be able to track those post marketly in case there was design changes to the lasers, if there was design changes to the fiber optics, if there are new indications for use to come along with a different drug. We needed a way to be able to at least track the devices.

For the drug company, of course, they wanted to not have anything to do with the devices after the fact. Historically actually what has happened since then is we have had two new indications for use added to the devices since the original approval, and the fiber optic systems have had three PMA supplements for design changes in the fiber optics.

This has made it much easier for them to make these changes to the devices because they could

come directly to a device document that existed, and it makes it easier for the Center for Devices to track these changes, and this is why we've done it.

That process has continued for subsequent drugs. Presently we have three approved photodynamic therapy device-drug combinations. The original one, which was by QLT, was for palliative treatment of esophageal carcinoma. The second one is for a topical drug for treatment of actinic keratosis, where we've done the same process where the NDA was submitted. We pulled out the device section, created a PMA for the light system, and we have continued to follow that device separately, and we have some suggestions again that the company has come in subsequently to the original approval and made a device modification to that device under the PMA as a PMA supplement, which again allowed that to work very smoothly for us.

And then the most recent approval, which I cannot remember now, is like three or four years ago. It was again from QLT for the treatment of age related macular degeneration, again using a laser

light source with a drug, which again we created the PMA process.

We've found that to work very well because in most cases so far, lasers have been the light source of preference because most of these systems so far require the ability to transmit light down fiber optics, and lasers give you that very nice ability to do that.

It has also allowed these companies to sell off the laser part of their approvals so that they don't have to be laser manufacturers.

Whether or not that's the future to where we will continue I have no way of knowing because the laser is a very unique part of this system and has unique responsibilities with the CDRH requirements under the light performance standard, but this history for the photodynamic therapy is how we got to where we are today with what we're doing. It is mainly because this was the first one of these to come into the system in 1978 actually, and when we first started this process, we had no previous histories.

And it did require a lot of collaboration between the Center for Drugs and the Center for Devices, and I will repeat what everybody else is telling you. With these kinds of products you have to get involved with the centers early on in discussions to find out not only where you're going to be placed as far as jurisdiction, but to find out from the reviewing centers what are going to be your responsibilities.

And I thank you for your attention.

(Applause.)

MR. JENKINS: Thank you, Richard.

Our last speaker is Dan Shames, who is the Director of the Division of Reproductive and Urologic Drug Products in CDER, who is going to talk to us about his experience with contraceptive delivery systems.

Dan.

DR. SHAMES: Thank you.

I just noticed that the title of this conference is "Innovative Systems for Drug Delivery." I'm the only person from CDER talking

about the drug portion of the review, and I'm the last speaker. So I guess this is what everybody is waiting for right here.

I want to thank the device folks for asking us to give our perspective on the review of drug device combinations. I'm going to discuss the particular experiences of our division in this area. I think our group has a particular interest and perhaps expertise since the gynecologists and urologists in our division have significant clinical experience with devices and drug-device combinations.

I was asked to evaluate our review process regarding contraceptive implants, and actually let me go back. I was asked to review contraceptive implants, but what I did was I expanded this to contraceptive drug-device combinations and other devices that we've had experience with in our division.

I'm going to take the experience that we've had over the last five or six years and give you what lessons we've learned regarding these

combination products.

I'm first going to describe five contraceptive systems that involve cooperative review of device and drug components. The approval year is in parentheses. The first are a group of device drug combinations that are all variations of subdermal progestin releasing implants for contraception. They deliver the drugs systemically. These are rods that are made up of a co-polymer core surrounded by thin walled elastic tubing.

I think that the lesson I got from this group was my personal education regarding the chemistry and the sort of engineering and pharmacokinetic experience related to quantifying manufacturing processes. So I personally learned a lot, and our division learned a lot by reviewing these materials.

Now, all of these and all of the products I'm talking about went through the same type of clinical trial experiences that oral contraceptives would go through. So the review standard was the same for these products as they

would be for any other kind of contraceptive device.

Next is Lunelle, which is a monthly injectable that delivers a combination of estrogen and progestin for contraception. The take-away message here is that although this was a prefilled syringe and should have been fairly straightforward, there were issues related to manufacturing the syringe and the vial,. et cetera, which did make the review challenging.

The other thing that should be a lesson here is that there were two drugs involved, and we had to deal with the combination rule regarding drugs in themselves. So we not only dealt with the device issue. We dealt with the fact that we have to show that each individual drug adds to the safety and efficacy of the product.

Mirena, which is the next one, is an intrauterine system which delivers levonorgestoral both locally and systemically. I think the important take-home message for this one is that although there have been IUDs around for some time, there was a challenge here to show that the addition

of the drug added to the effectiveness and safety of the product itself, which is something that products have to do, combination products have to do in general.

This next one is an intravaginal ring, which delivers estrogen and progestin systemically. This was relatively recently approved. It can be inserted by the individual themselves. Vaginal contraceptive rings have been studied for decades, but it took some innovation on the part of the developer to get it quite right regarding both placing the estrogen and the progestin, and the right combination of materials to make this work properly.

I think this is our last example. This is a transdermal system which delivers estrogen and progestin, and although you might think at first glance, well, this, you know, should be fairly easy, we have a lot of transdermal systems. We've had transdermal systems for menopausal symptoms for many years, but as you may or may not realize, it requires more drug delivery for contraception than

for menopausal symptoms, and it took some significant innovation for the developer to create a system which is only about the size of a match box and deliver the appropriate amount of estrogen and progestin.

So I was asked to look at all of this and look at our experience and ask myself what did we learn from this. Well, the good news is that as far as CDER, we can work with device technical experts in a productive and efficient manner to review innovative drug delivery systems, and we have done it, and we continue to do it, and most of the time it goes fairly well.

In this case, with contraception, it was relatively easy because we used the same standards for review, the same clinical trial standards, and that was not terribly burdensome on the device systems.

And also, as many people have said, it goes much better when we discuss these issues a priori, before we start.

The other news, the good news and then

the other news, when it doesn't go well. It doesn't go well, I find, when things are a little out of the box, which, of course, is happening more and more. I find that at least with our division the problem is not necessarily the scientific challenges. It's how to fit the scientific issues into the regulatory constraints that we all seem to have, and I think that's improving.

Then, of course, we have the issue about who's in charge, which we've talked about, CDER or CDRH. I've never seen a turf battle, but I guess that could possibly happen.

We also have what I call culture clashes, and I didn't see Mark's slides. He calls it war of the worlds or colliding of the worlds. Sometimes critics of CDER might characterize our reviewers as what I have here, the pointy headed bureaucrats whose main goal is to keep things off the market because they have no regard for the entrepreneurial spirit and good old American ingenuity. We're just obstructionists, et cetera, et cetera, you know, versus the critics of CDRH who

think the reviewers are those people who will approve anything that doesn't blow up when they plug it in regardless of consequences to patient safety.

Of course, none of that is true, but there is a bit of a culture clash, and you know, I try to think what is the origin of this culture clash. Well, maybe it's engineers and doctors, you know. There's a lot of doctors in CDER. There's a lot of engineers in CDRH, and I really don't think that's the basic -- I think it's a matter of working together more because the doctors in CDER seem to get along well with the chemists, which we deal with. We've had a long history with, and I just think we should be able to get along with the engineers also.

Perhaps another issue that may be more important has to do with this reasonable versus substantial evidence, which is in our regulations. I'm not sure that's supposed to be an issue. I've had sponsors and lawyers for sponsors tell me, well, that's only in the eye of the reviewer, you know. You determine what's reasonable and substantial.

And then there's the issue of the big PhRMA versus small firms, and it is true that we deal with larger companies in general, but we do deal with smaller companies, and I think that's something maybe we all have to learn how to deal with better.

However, the future looks good in my estimation. I think Mark's group has actually improved things. We've had a very difficult issue that had been essentially in regulatory and scientific limbo for years, and Mark was able to get us to move forward on this issue, find a way to move forward, and I think the regulatory hang-ups can often be the most difficult hang-ups.

I think we are improving in terms of the culture gaps or culture differences between the two areas, and I think getting the message out that we have to be talking about development very early on with companies is important.

However, I think most staff at CDER and CDRH enjoy working on innovative products and are well motivated to assist the sponsors and improve

our internal processes.

Thank you.

(Applause.)

MR. JENKINS: All right. Thanks, Dan.

I guess we're done with this section, and we'll move on to the panel discussion.

DR. JACOBSEN: While she's collecting the questions, let me just welcome everybody back to this final session where we have both FDA and industry on the panel up here. We have tried to put FDA and industry folks on both sides of the table so that we're coming across with a message that this is not an us against them. This is an exciting new area or an exciting old area really if you listened to Richard Felten, and just listening to the talks this morning, it was, I think extremely exciting to see all of the things coming down the road.

Clearly, we're going to have lots and lots of issues to work through together, and I think together ought to be the underlying take-home message from today.

I have one. Do you have more written

questions?

I think the appropriate thing to do is this is your part of the meeting, to let people ask questions, and as I said before, you can either walk up to the mic and ask it out loud or you can send your question up on paper and we'll try to, you know, get them answered.

I mean, I can do a kick-off question from the paper if that makes everybody more comfortable. I have one.

Miriam, do you have something?

Stuart, go ahead.

DR. PORTNOY: Hi. My name is Stuart Portnoy, and until a year ago I worked at CDRH for eight years, most recently as a Branch Chief of International Cardiology Devices.

While I was at the FDA and in the past year since I joined PharmaNet as a medical device consultant, I have closely monitored the regulatory and scientific requirements for drug-device combination products, especially drug eluting stents.

And it has been my observation that while CDRH has been designated as both the lead review center and the regulatory authority for drug eluting stents, the agency has clearly and consistently raised the bar so that these products are actually regulated more like drugs than devices.

I'm concerned that if this trend were to continue, that some new and potentially breakthrough combination technologies may face significant delays in making it to the marketplace and putting it to clinical use because of unrealistic agency expectations and requirements.

And specifically, I've noticed a trend of what I consider to be overly burdensome requirements for things like kinetic drug release testing, stability and lot release testing, and other traditional drug testing requirements.

Now, while I agree with the FDA that such testing is absolutely necessary and fundamental to demonstrating acceptable product performance, I still believe that the agency is already going too far in their requirements that the drug-device

combination products are held to the same standards and level of quality control as pharmaceuticals.

And let me emphasize that this is for drug agents that have previously been demonstrated to be safe in an NDA.

So to address this concern, I hope and recommend that the agency and specifically the Office of Combination Products considers a reasonable and feasible approach to regulating combination products that lies somewhere between the current requirements for traditional pharmaceuticals and perhaps the less burdensome standards for medical devices, and I invite panel discussion of this important issue.

DR. JACOBSEN: Just let me add that we are joined at the panel -- I should have done this before -- we have two center Directors joining the panelists who have already spoken here today: David Feigal, the CDRH Director, and Jesse Goodman, the CBER Director. Obviously they really need no introduction, but I figured I'd better do it anyway.

Anybody want to start off with that?

DR. FEIGAL: Well, let me make a comment. I don't think the standards are the same. If the standards were, then some of the things you have asked for would not get alternatives. If you didn't understand the release kinetics and couldn't do bridging between release kinetics of two formulations, the only thing you could do if you changed manufacturing would be to repeat the clinical trials.

And so I think there is a real vested interest for us to make this as scientifically based a process as possible because we have not taken that stance, nor have we taken some of the other types of traditional pharmaceutical approaches of requiring the manufacture of three complete commercial batches prior to NDA approval. We haven't required only testing, only doing clinicals on products manufactured in the final formulation.

So I think there still is a fair amount of flexibility there. The one sort of wish that we often hear is to say we'd like to have a breakthrough product, and we'd like to not have to

submit any evidence for it.

(Laughter.)

DR. FEIGAL: And to me it has always struck me as sort of strange when someone says we have enough evidence to show that it's safe, but this is a breakthrough product and we haven't seen the evidence of effectiveness yet.

It would strike me that if you've got enough evidence for safety so that you've begun to see what the side effects are and so that you're seeing side effects but you haven't seen any benefits yet, you must not have a positive risk-benefit ratio.

So I think that all of the centers, when you have a product that's dramatically different than the existing therapies, treat those products differently. The evidence requirements are generally less, and I think it would have been a mistake to have simply stopped with the European experience. The limitations there weren't so much the small numbers, but the very careful limitation of the types of patients studied and have led the

public to believe that that's the expectation of what to expect from the product.

There's a need to characterize how these products basically work. In other words, I think, you know, we can join the advertising promotion staff of the companies, as many of our former employees do.

(Laughter.)

MR. HUNTER: Richard Hunter, and I'm not a former employee.

(Laughter.)

MR. HUNTER: I have been in the business for 35 years in industry to get products on the market, but just to ask my question, can you use your imaginations here to determine how a company like mine, Altea Therapeutics, that has a technology for delivering drugs and other products through the skin, can avoid double jeopardy, triple jeopardy, whatever, every time we go to a different division, a different center, which we will and have to some degree already?

In terms of some of the major questions,

I know that there will be tailored questions per patient group and per drug, but the major questions, the blockbusters that would put us back to square one in that particular area. Can you imagine a better world, is what I'm asking.

MR. KRAMER: I think we can imagine that world. If I understand the question correctly, I guess what you were indicating was that when you have a new indication for an existing product, that that indication is going to different divisions within a center, and therefore, new questions are generated each time.

I think the intent would be not to have to, you know, reinvent the wheel. We've heard that before. If that's a problem that you're encountering, then you should definitely bring that to the agency's attention so that we can look into that.

I mean, clearly indication-specific questions will arise, but if fundamental questions, as you say, have been answered, then I don't think the intent would be to have to review those all over

again.

DR. JACOBSEN: Okay.

DR. GOODMAN: I'd just make one addition, which is certainly in our world you can refer to master files and data generated in other settings to support an application involving portions of the same product. So to the extent that the developers of these products are the same or are cooperating, you know, we're very open to looking at data broadly, but as Mark said, there are going to be some kinds of data that are distinct for a new combination.

DR. VAN ANTWERP: We've talked a lot about today --

DR. JACOBSEN: Could you identify yourself?

DR. VAN ANTWERP: Oh, I'm Bill Van Antwerp from MiniMed, Medtronic MiniMed.

We've talked a lot today about drug delivery systems, but we all, or at least those of us in the diabetes world, believe what David showed us this morning, that devices delivering drugs or