FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACY COMPOUNDING ADVISORY COMMITTEE (PCAC)

Tuesday, November 21, 2017

8:30 a.m. to 11:19 a.m.

FDA White Oak Campus

White Oak Conference Center

10903 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Cindy Chee, PharmD

Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

PHARMACY COMPOUNDING ADVISORY COMMITTEE MEMBERS (Voting)

Robin H. Bogner, PhD

Professor

University of Connecticut

School of Pharmacy

Department of Pharmaceutical Sciences

Storrs, Connecticut

Michael A. Carome, MD, FASHP

(Consumer Representative)

Director of Health Research Group

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Gigi S. Davidson, BSPh, DICVP

(U.S. Pharmacopeial Convention Representative)

Director, Clinical Pharmacy Services

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Kuldip R. Patel, PharmD

Associate Chief Pharmacy Officer

Duke University Hospital

Durham, North Carolina

Allen J. Vaida, BSc, PharmD, FASHP

(Participation in L-citrulline, pregnenolone, astragalus, epigallocatechin gallate, and resveratrol discussion)

Executive Vice President

Institute for Safe Medication Practices

Horsham, Pennsylvania

Donna Wall, PharmD

(National Association of Boards of Pharmacy Representative-Participation via phone)

Clinical Pharmacist

Indiana University Hospital

Indianapolis, Indiana

PHARMACY COMPOUNDING ADVISORY COMMITTEE MEMBERS

(Non-Voting)

Ned S. Braunstein, MD

(Industry Representative)

Senior Vice President and Head of Regulatory Affairs

Regeneron Pharmaceuticals, Inc.

Tarrytown, New York

William Mixon, RPh, MS, FIACP

(Industry Representative)

Former Owner

The Compounding Pharmacy

Hickory, North Carolina

C O N T E N T S

P R O C E E D I N G S

(8:30 a.m.)

Call to Order

Introduction of Committee

DR. GULUR: Good morning, everyone. I would first like to remind everyone present to please silence your cell phones, Blackberries, and other devices if you have not already done so. I would also like to identify the FDA press contact for this open session meeting, Ms. Lyndsay Meyer.

Ms. Meyer, if you are present, please stand.

Good morning. My name is Padma Gulur. I am the acting chairperson of the Pharmacy Compounding Advisory Committee, otherwise referred to as PSAC. I will now call the committee to order. We will now ask those at the table, including FDA staff and committee members, to introduce themselves starting with the FDA to my far left and moving along to the right side, ending with one of the industry representatives, Dr. Ned Braunstein.

DR. DOHM: Julie Dohm, agency lead on compounding.

MS. BORMEL: Gail Bormel from CDER's Office of Compliance, Office of Unapproved Drugs and Labeling Compliance.

DR. LAWSON: Rosayln Lawson, Office of Compliance, also from OUDLC.

MS. ROTHMAN: Sarah Rothman, CDER's Office of Unapproved Drugs and Labeling Compliance.

DR. RUPP: Tracy Rupp, Office of Unapproved Drugs and Labeling Compliance.

DR. GHOBRIAL: Michael Ghobrial, CDER Office of Compliance, Office of Unapproved Drugs and Labeling Compliance.

DR. TYNER: Katherine Tyner, Office of Pharmaceutical Quality.

DR. CRUZ: Celia Cruz, Office of Pharmaceutical Quality within CDER and the Office of Testing and Research.

DR. VAIDA: Allen Vaida, committee member, pharmacist at the Institute for Safe Medication Practices.

DR. CHEE: Cindy Chee, designated federal officer for Pharmacy Compounding Advisory

Committee.

MS. DAVIDSON: Gigi Davidson. I represent the United States Pharmacopeial Convention.

MR. HUMPHREY: William Humphrey, director of pharmacy operations at St. Jude Children's Research Hospital.

DR. PATEL: Kuldip Patel, associate chief pharmacy officer at Duke University Hospital, representing hospital and health system pharmacy.

DR. BOGNER: Robin Bogner, member of the committee and professor of pharmaceutics at the University of Connecticut, School of Pharmacy.

MS. JUNGMAN: Elizabeth Jungman, director of public health programs at the Pew Charitable Trusts.

DR. HOAG: Steve Hoag. I'm a professor at the University of Maryland, School of Pharmacy.

DR. CAROME: Mike Carome, director of Public Citizen Health Research Group.

MR. MIXON: Bill Mixon, compounding pharmacist from Hickory, North Carolina and nonvoting industry representative.

DR. BRAUNSTEIN: Ned Braunstein, senior vice president for regulatory affairs and pharmacovigilance and risk management at Regeneron Pharmaceuticals. I'm the pharma industry representative on the committee, nonvoting member.

DR. GULUR: Thank you. Dr. Wall, on the phone, could you introduce yourself?

DR. WALL: I'm Donna Wall. I'm the NABP representative on the committee, and I'm a pharmacist.

DR. GULUR: Dr. Desai I believe is not joining us at this meeting, and Dr. Venitz is not joining us.

We will continue. For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these ideas and that individuals can express their views without interruption. Thus, as a reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look

forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media may be anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch.

This morning, we will discuss liposome drug products and drug products produced using hot melt extrusion, which were nominated for the Difficult to Compound List. For each topic, we will hear presentations from FDA, ask clarifying questions of them, hear nominators' presentations, ask clarifying questions of them, hold an open public hearing, and have committee discussion and voting.

Let us begin. We will now have Dr. Cindy

Chee read the Conflict of Interest Statement.

Conflict of Interest Statement

DR. CHEE: The Food and Drug Administration is convening today's meeting of the Pharmacy Compounding Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the National Association of the Board of Pharmacy, the United States Pharmacopeia, and the industry representatives, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with the federal ethics and conflict of interest laws, covered by but not limited to those found at 18 USC Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in

compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, speaking, teaching, writing, patents and

royalties, and primary employment.

Today's agenda involves discussion of liposome drug products and drug products produced using hot melt extrusion for inclusion on the Difficult to Compound List. Drug products produced by extrusion or nanotechnology were nominated for inclusion on the Difficult to Compound List. Nominators were invited to make a short presentation supporting the nomination.

This is a particular matters meeting during which general issues will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the topic at issue.

We would like to note that Dr. Donna Walls is a representative member from the National Association of Boards of Pharmacy and that Ms. Gigi

Davidson is a representative member from the United States Pharmacopeia.

Section 102 of the Drug Quality and Security Act, amended the Federal Food, Drug, and Cosmetic Act, with respect to the advisory committee on compounding to include representatives from the NABP and the USP. Their role is to provide the committee with the points of view of the NABP and USP. Unlike the other members of the committee, representative members are not appointed to the committee to provide their own individual judgment on the particular matters at issue. Instead, they serve as the voice of the NABP and USP, entities with financial or other stakes in the particular matters before the advisory committee.

With respect to FDA's invited industry representatives, we would like to disclose that Dr. Ned Braunstein and Mr. William Mixon are participating in this meeting as nonvoting industry representatives acting on behalf of regulated industry. Their role at this meeting is to represent industry in general and not any

particular company. Dr. Braunstein is employed by Regeneron Pharmaceuticals and Mr. Mixon is employed by The Compounding Pharmacy.

We would like to remind members and temporary voting members that if the discussion involves any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have regarding the topic that could be affected by the committee's discussions. Thank you.

DR. GULUR: Thank you, Cindy.

We will now hear the FDA presentation on liposome drug products from Dr. Tyner.

FDA Presentation - Katherine Tyner

DR. TYNER: Good morning, everyone. My name is Katherine Tyner. I am the associate director of science in the Office of Pharmaceutical Quality in

CDER. I am also the center lead for the working group for drug products containing nano materials of which many, but not all, of the liposomes we'll be talking about today fall into.

I have with me today also two additional subject matter experts in liposome drug products. I have Dr. Xiaoming Xu from the labs in Office in Testing and Research, and from the review side, Dr. Hailing Zhang from the Office of Life Cycle Drug Products. And both of them will be available for the question and answer session following this talk.

I'm going to go into a couple of slides on background for liposome drug products, and then we'll get into the actual evaluation criteria about why we believe these are difficult to compound.

Liposome drug products. There is a draft guidance for industry that was revised in 2015 on liposome drug products, and within that guidance, liposomes are defined as microvesicles composed of a bilayer and/or a concentric series of multiple bilayers separated by aqueous compartments formed

by amphipathic molecules such as phospholipids that enclose a central aqueous compartment. And that is many words to describe what this diagram shows so nicely.

You're going to have a molecule that has a polar head group and a hydrophobic tail. This bilayer is also called a lamellar bilayer. It's hydrophobic. You can do other things such as put cholesterol within the lipid bilayer that's going to change the membrane fluidity, change drug-release characteristics. You can change the surface by putting on things like PEG or targeting molecules. We'll be going all into this in detail in the following slides.

You can also put drugs in these vesicles, so you can have a hydrophilic drug that goes into the aqueous core, or you can have a hydrophobic drug that goes into the lipid bilayer. That guidance also defines a liposome drug product, which is a drug product in which the active pharmaceutical ingredient, which I will now call API for the rest of the talk, is contained within the liposomes.

And for this review, we are also considering if the API was supposed to go into the vesicle but for whatever reason did not.

Liposomes are a fairly complex structure, as you can see here, and it's important to note through the scope of this consult that you can have all of the ingredients you need to make a liposomal drug product, put it into a pot and stir it, and at the end not come out with a liposomal structure. You get something like a solid lipid nanoparticle, or you could get a micelle. You could get an oil and water emulsion. You could get globules.

All of those structures would not fall under the scope of this consult. We're only talking about when we have these liposome structures here.

Structurally, the liposomes are composed predominantly of phospholipids arranged in a bilayer configuration. We're going to be talking a lot about the phospholipids and this bilayer configuration because it's going to be very important for controlling the drug release, for controlling the stability of the vesicle. We're

also going to be talking a lot about the size of these vesicles. The size of liposomes can range from about 20 nanometers to over 1,000 nanometers.

Now, if you have liposomes below 1,000 nanometers, they can fall under the agency's Points to Consider for Nanotechnology, which is described in our final guidance. The reason why I mention this is for drug products containing nano materials, liposome drug products are among the most commonly approved drug products containing nano materials. So you've seen a lot of them come through as drug products containing nano materials, but again, not all liposomes would necessarily trigger those to points to consider as detailed in the agency guidance.

The size is going to be very important for these vesicles. It's going to impact biodistribution. It's going to impact stability and many other things. The third real key, which is going to be impacting the complexity of these products, is the modification of the surface characteristics. You can change the surface, and

that's going to impact circulation time, targeted delivery of the liposomes, and other factors which we'll go into shortly.

The first FDA approval of a liposome drug product happened in 1995. It was Doxil. Since then, there are 11 FDA-approved drug products containing liposomes. They're administered either by intravenous, epidural, or intrathecal injection, and the indications range from cancer to fungal infections to pain.

They're very versatile in nature, and one of those reasons is because you can attract both hydrophilic or hydrophobic APIs, and sometimes both together. These vesicles are commonly used to alter the biodistribution of an API, and they've been shown to improve drug dissolution, stability, deliverability, and many other aspects of the drug product.

That's the background. Now we're going to get into the difficult to compound criteria, and the first are the complex formulations. Factors that are known to demonstrate formulation

complexity and their impact on product performance include the lipids, the other inactive ingredients, and the overall vesicle stability.

Let's talk a little bit about the lipids. The structure of the lipids can impact the overall lipid function and stability not just of that lipid but also the entire vesicle. When you have these phospholipids, you have a hydrophilic head group, a polar head group; you have the hydrophobic tail; and you have a linker which links the two together.

The hydrophilic head group, this is going to be what the body sees. It's going to be on the outside of that vesicle, so it will be interacting with liposome membrane interactions and will also impact drug permeation across barriers. The hydrophobic tail can impact stability, and the linker, such as ether and ester, can impact whether or not your liposome is biodegradable or not.

The lipids can also impact safety, and this is something we'll come to several times during this talk. If you have a double-tailed lipid -- and this is an example here where you have

two chains of the hydrophobic tail. If you have a double-tailed lipid, if there's chemical degradation, which causes it to become single-tailed, you can form a lysolipid. Why is that important? Lysolipids can bind to red blood cells, and they can cause hemolysis, and ultimately cause a safety signal for the patients.

The inactive ingredients of lysolipids are going to be very important, but there are also other inactive ingredients that an also impact the ultimate product performance, safety, and efficacy of these products. For example, many liposomes contain cholesterol, which can impact the fluidity of the membrane, and it impacts the drug leakage and the stability overall of the vesicle. You can have polyethylene glycol also termed PEG or PEG derivatives. This is used to passivate the surface and promote longer blood circulation times.

The concentration of the inactive ingredients, the lipids to these other materials, ends up usually being a critical factor that impacts the safety, efficacy, and stability of

these products. In addition, the grade of the lipids also can impact the performance as well. It's been shown to impact the PK and PD performance of the product.

You also have the overall vesicle, and that overall vesicle can have stability issues, both chemical and physical, and these can be due to formulation related factors such as the size and size distribution of the vesicles, the ultimate morphology if it's a true sphere versus a distorted sphere, surface coating, pH, buffer, or counter ions.

The structural integrity of the liposomes can be compromised, and they can form different structures. You can have lipid fusion, where you have the vesicles actually fused together to form a larger vesicle. You can have aggregation where they're not actually fused but they're associated together. And you can have leakage of the contained API during storage, and that's something that will be a repeated scene when we talk about the safety of these products.

Concluding for the complex formulations, the selection of lipids for formulating the lipids can impact the finished product for quality, safety, and performance. The other inactive ingredients impact the physicochemical properties of the liposome drug product, which in turn can impact the pharmacokinetic and pharmacodynamic profile and behavior. The formulation related factors can impact the physical chemistry and stability of these drug products, ultimately meaning that the complexity of these formulations present a demonstratable difficulty for compounding.

Let's talk about drug delivery mechanisms. To achieve the proper performance of these products, the liposomes need to be designed to release the API contained within the liposome in a predictable manner, and that predictable manner should be stable throughout the shelf life as well as the in-use conditions. This is going to be really important when we're really talking about preventing off-target or premature drug release in any type of administration.

Different delivery profiles and different delivery mechanisms can be achieved by the different lipids and appropriate production processes. Factors that are known to have a substantial impact on the complex nature of the drug delivery mechanisms include interactions with the liposomes in the body, physicochemical properties, and the lipid composition.

Now, as I mentioned, what we've seen right now coming into the FDA for approved products, they are all going through some type of needle, but this complexity does apply for all potential routes of administration.

Let's talk a little bit about some of these complexities. Looking at the liposome blood component interactions, in order to ensure a predictable drug delivery with liposome drug products depends on the balance of interactions between the liposome carrier system and how it is interfacing with the body. If we're talking about in the blood, there are lipid proteins, there are opsonins. So those are going to be proteins that

can coat the outside of the lipid vesicle, and all those can ultimately impact how that vesicle is performing in the body.

This opsonization where you have these proteins forming what is usually termed a corona, that can be altered based on what the surface of the liposome looks like, the composition, the size, and the surface characteristics, and that can ultimately impact how that liposome is behaving within the body.

These interactions oftentimes are desirable and help facilitate the delivery of the API, but if they're not controlled, they can lead to undesired release of the API. This becomes important, again, when we're talking about patient safety because liposome drug products generally incorporate a higher dose of API than traditional dosage forms. So if you have an undesired release, especially if you have dose dumping where you suddenly have a burst release of this API, you can lead to exposures at toxic levels of the API.

The rate of in vivo release depends on the

API's physicochemical properties, the loading mechanism, how the drug is introduced into the liposome vesicle, the location and the state of the entrapped drug, whether or not it's crystallized or not, again, the lipid composition, and the internal environment; so what that actual aqueous compartment in the middle of the liposome looks like.

On the right-hand side, we have an example from the lab, and this is a collaboration that was done within the FDA and one of our academic collaborators that looks at that interplay between the different inactive ingredients, the phospholipids and different excipients, and showing how just changing the ratio has an impact on the drug release.

The mechanism by which an API is released from a liposome drug product involves precisely designing and formulating the system that delivers a specific amount of API per unit time and usually into a specific region of the body. The in vivo biodistribution and release are affected by

multiple factors, and for these reasons, the complexity of the drug delivery mechanisms of the liposome drug products presents a demonstrable difficulty for compounding.

Complex dosage forms. Again, the ones that we've seen already coming through the FDA and being approved are coming in either as suspensions or lyophilized powders for suspensions. The characteristics of the physical dosage units of the liposome suspensions or powders for suspension can be difficult to consistently achieve and maintain; so making sure that you have a well-defined particle size and particle size distribution; the status of the API, so whether or not it's actually contained in the liposome like it's supposed to be; and the surface chemistry of the liposomes.

These characteristics have a significant impact on the safety and effectiveness of liposome drug products, and various formulation components, including inactive ingredients, end up playing a critical role in the dosage form performance and stability. Keeping in mind that for an injectable

versus some other route of administration, you can have different inactive ingredients, and those are going to have a critical role and interplay for these liposome drug products.

You need extensive product development and precise control over the raw materials in optimizing the process parameters in order to make sure that you've produced a safe, effective, and high-quality liposome drug product. For these reasons, the complexity of the dosage form presents a demonstratable difficulty for compounding.

Bioavailability. This is my second favorite topic. When you administer a liposome drug product into the body, a couple of processes are going to occur, which include delivery to the tissue and also elimination. You can have tissue uptake of that entire liposome drug product where the vesicle and drug are together. You can have the API released from the liposome and have that API floating around and doing its own thing. You can have clearance of released and unbound API leaving the body. You can have clearance of that whole

liposome drug product vesicle, and you can have clearance of that drug carrier in an empty state.

There are many different forms, and all of them are going to have different ADME, absorption, distribution, metabolism, and elimination. It's a non-trivial exercise to determine which form the drug is actually in within the body, and that makes it complex to characterize and also control bioavailability. You can also have, again, those interactions between the blood proteins and lipoproteins, which can cause dose dumping, which have the safety implications for the patient.

Because of the complexity of the interactions between API released from the liposomes and tissue uptake, just simply measuring the total API in a certain organ doesn't necessarily reflect what's going on with this drug system, so it may not reflect bioavailability of the API at the intended target or site of action.

Biodistribution and the release of the API can be impacted by very subtle changes to things such as the formulation composition, the purity of

the lipid as a raw material, and the manufacturing processes. All of this can influence the availability of the API in systemic circulation, or at the tissue, or even at sub-cellular targets. Characterizing and controlling the bioavailability of liposome drug products is complex and presents a demonstratable difficulty for compounding.

Complex compounding processes, again, many, many words, though on the right-hand side is a table which goes over different manufacturing methods for liposome drug products and some of the critical process parameters that are typically looked at for in-process controls for these drug products.

On the left-hand side, it is summarized and has pulled out some of the key things. You have the formation of the liposomes. You have to form the liposome if you're going to have a liposome drug product. Things like temperature of the aqueous phase is going to impact things such as particle size and particle size distribution.

Typically, once you have your vesicle,

you're going to go through a size reduction that's called typically homogenization. Speed, time, temperature all influence the mean particle size, which again can in turn affect product performance.

Loading of the API. You have your liposome, and that's awesome. You now need to make sure that the drug goes into it. Things that can impact that; temperature during the loading process can impact both the encapsulation as well as loading efficiency.

Purification, many of the ones that we're seeing are injectables, so it's critical to have them sterile, so you have a terminal sterilization step. It's critical to make sure that any purification procedure doesn't adversely impact the quality and performance of the liposome drug product.

Now, what do I mean by that? Let's say that you have a terminal sterilization procedure that has maybe a lipophilic membrane that you're going to then use as your terminal filtration process. If it's a lipophilic membrane, you could actually

strip out the lipids of your liposome and completely destroy the structure of the liposome. So you do need to make sure that you still have that structure that's going to be delivered to the patients.

Quality of the produced liposome drug products tend to be highly dependent on the process parameters, including extrusion membrane pore size, and this is during the homogenization; extrusion pressure; temperature; and the number of cycles you go through.

Something to note is that when you have a freshly prepared API containing liposomes -- when you have a freshly prepared liposome that has a drug substance, it's always going to contain some unencapsulated API, and this can cause some stability issues because if the API's just floating out there, you can actually have it interacting on the surface of the liposome such as charge interactions and cause instability of the liposome vesicle. If you have unencapsulated API, you can also have unwanted systemic toxicity upon

administration because you have, again, that high exposure of the naked API. Usually filtration and/or dialysis are used to remove unencapsulated API, but again, you have to do that next step to make sure that process hasn't completely messed up your liposomes.

Quality of liposomes may also be impacted by changes in manufacturing scale, so things that can be impacted during scale-up include shear, pressure, temperature, batch-size related hold times, and the lyophilization parameters.

Overall, poor control over the unit operations can lead to a variability in product quality, which may potentially lead to a negative impact on product efficacy and safety. Producing liposome drug products involve complex compounding processes that present demonstratable difficulties for compounding.

This is my favorite section, which is physicochemical testing. We're going to talk a little bit about particle size. We've mentioned it a lot over the past slides. Particle size is

almost always a critical quality attribute for liposome drug products. The reason for that is it impacts your ADME, it impacts your stability, and it impacts your drug release.

It impacts biodistribution, the drug pharmacokinetics, and often ends up being a critical determinant of product efficacy and safety, so oftentimes we like to have it measured, sometimes multiple times in different ways. There are many different ways you can measure liposome particle size, and all of those methods are going to have their pros and cons, and they're all going to have some type of sample preparation, which itself can impact the actual test results.

For that reason, many times it's requested that multiple techniques, such as dynamic light scattering and electron microscopy are used in tandem to thoroughly characterize the particle size and particle size distribution.

I have two beautiful examples here. The bottom is cryo transmission electron microscopy, and this is of a liposome drug product. You can

see the drug is crystallized within the vesicle, and you're forming a distorted sphere. Actually through TEM, you can actually not just see the size and size distribution; you can also see the morphology, so you can see that it's distorted. If you look really, really closely and if you zoom up, you'll be able to see the bilayers. You can see if there's more than one bilayer.

So you get a lot of information from the cryo TEM, but oftentimes we're also looking at different methods such as light-scattering methods.

This is an example of a dynamic light-scattering method, and this is actually the same product. It's the same run. It's the same substance, and these different traces are just using different algorithms to calculate what the result is for the particle size. So it's the exact same product, but you can see, if you look at one, you have a very nice monodispersed system, and if you look at the other ones, you start seeing that you have larger particles and much more polydispersed.

So not only how you're measuring these products, but also how those measurements are being reported can impact the ultimate results of your product.

Particle size is very, very important, but it's not the only important thing. We've mentioned the lipids excipients are critical raw materials, and they can impact the quality and performance of the drug products. Typically, you need to have detailed information, such as the manufacturing characterization and controls of the lipids. Specifications for lipids include but are not limited to the source, the physicochemical characterization and the degradants, especially those lysolipids.

With respect to those degradants, complete degradation profiles are usually needed to accurately determine a potential safety risk of the product, and that's usually controlled not only in process by also in the shelf life as well to make sure you don't have an excessive amount of lysolipids at the end of shelf life.

Drug release. Liposome drug products usually include an in vitro test for the release of API from the liposomes. This is used to evaluate product quality, suitability of in-process controls, and the influence of different CME changes on product quality. This in vitro release method should be able to discriminate between acceptable and non-acceptable batches of the drug product.

Those are the three big ones: the size, the lipids, and the drug release. But there's also a whole host of other different characterization that needs to happen for these drug products. Some of them are easier than others to do, but things such as the morphology of the lipids, including how many lamellars you have; surface characteristics; structure and integrity; parameters of the contained drug, so how much you actually have in the vesicle; the drug loading; leakage rate tends to be a very big one; as well as the liposome integrity itself.

Suitable analytical methods need to be

employed to properly characterize liposome drug products, which can often be difficult given the complexity of the actual formulation. Use of inappropriate methods could produce false results, which actually call into question the data reliability and ultimately the product quality. For these reasons, physicochemical and analytical testing for liposome drug products are complex and present demonstratable difficulties for compounding.

Talking a little bit about the risk-benefit to patients, compounded drugs are not FDA approved but they can serve as an important role for patients whose clinical needs can't be met by an FDA-approved drug product. Liposome drug products do present a significant safety risk for compounds given the complexities that I've talked about. Many of the APIs used in liposome drug products are cytotoxic, and if the API is not encapsulated properly or is released prematurely, the product can at best be ineffective and at worse be hazardous. The risk to patient safety of

compounded liposome drug products outweigh any potential benefit of increased patient access.

Getting into the recommendation, liposome drug products present demonstratable difficulties for compounding that reasonably demonstrate and are reasonably likely to lead to an adverse effect on the safety and efficacy of such products. Taking into account the risk and benefits to patients, we do believe that liposome drug products should be included in the Difficult to Compound List under Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act.

Clarifying Questions from the Committee

DR. GULUR: Thank you.

At this time, we will accept clarifying questions from the committee. We ask that you limit your questions to clarifications only. Members will have further opportunity for discussion and questions after we have heard all of the presentations. Dr. Vaida?

DR. VAIDA: The only products currently approved are injections, either intravenous or

epidural?

DR. TYNER: Intravenous, epidural, and intrathecal are the three.

MS. JUNGMAN: Clarifying. In your evaluation, were you looking at liposomal drug products that were approved or were you also looking at the way that they're used in compounding currently?

DR. TYNER: We were looking at all liposome drug products, not just the ones that were approved.

DR. GULUR: Dr. Braunstein?

DR. BRAUNSTEIN: That's what I was seeking clarification on. Can compounding produce liposomal products for other types of uses? For example, is there any reason to use them in a topical formulation? Would there be other drug products? I know you listed the ones like chemotherapy agents, amphotericin, things of that nature, but would there be a reason that you couldn't or might want to put a compounded product in a liposome that was not one of those agents,

some other drug? I'm asking you this question.

DR. TYNER: Tracy, did you want to answer?

DR. RUPP: Sure. I'll just give you a little information. We think that many of the products that are currently made by compounders, for example those that might be called liposomal creams, may not meet the definition of liposome drug product as defined in the consult or in the review. For example, the products may not contain liposomes or the API may not be contained in a liposome.

DR. BRAUNSTEIN: If that was the case, then those products would not be on the Difficult to Compound List. Is that what you're saying? In other words, the only products that you're seeking to put on the Difficult to Compound -- or the only process, rather, I should say that would be on the Difficult to Compound List is this specific process that we're discussing today and not perhaps what some other people might call liposomes.

DR. RUPP: Right. We're seeking to put on the list the liposome drug products as we've

defined them here in this consult.

DR. GULUR: Dr. Davidson?

MS. DAVIDSON: In slide 3, your definition of a liposome drug product, is that statutory? Because that's a pretty broad definition.

DR. TYNER: It is an agency guidance.

MS. DAVIDSON: Okay, because I share Dr. Braunstein's concern that there are lots of topical products particularly that are encapsulated in something that could be called a liposome for topical penetration enhancers, those sorts of drugs, and I would not want those to be included in this definition. But the definition that I'm reading from your slide could be interpreted to include those as well. So I'd like, for the record, it noted that those don't apply.

DR. RUPP: One other clarification I wanted to make, too, is as she mentioned, we are including products that are intended to be liposome drug products. So if a product is described in such a way that would meet the definition in this review, then it would also fall under the purview of what

we've described here.

DR. TYNER: Also just to clarify from a technical point, that definition 3 is talking very much about the structure. So as I mentioned, you can have all of the components be in there and not actually get that liposome structure.

DR. GULUR: Dr. Bogner?

DR. BOGNER: But if you make a claim of liposomal, even if you don't have that structure, because you intend to make the claim that it's liposomal, it is necessarily in this group of compounds, in this group of materials.

MS. BORMEL: That's correct. If you're intending to put the API in a liposome and call it a liposomal formulation, that would be covered by this review.

DR. BOGNER: So that includes the creams where that claim is being made.

MS. BORMEL: If you use the cream and you intend to put an API in the liposomes that are in that cream, it would be covered. But we're not even sure that some of the creams are actually

liposomes.

DR. BOGNER: I share your skepticism. I'm trying to determine, in terms of labeling and claiming, where the definition I guess is -- where that line is drawn. So if I have a liposomal cream -- if I have a liposomal vehicle and a compounder puts drug into it but doesn't claim that the drug is inside, then that is not part of this particular category that we're talking about.

MS. BORMEL: Correct.

DR. BOGNER: Thank you.

DR. GULUR: Dr. Mixon?

MR. MIXON: Dr. Tyner, what's the difference in a liposome and a micelle?

DR. TYNER: It's the bilayer structure. So you have the lamellar structure where you have the polar head groups on the inside and the outside. The micelle is just going to have the polar head groups on the outside.

MR. MIXON: Going to have what on the outside?

DR. TYNER: The polar head groups on the

outside and just the hydrophobic core on the inside.

DR. GULUR: It's not bilayer?

DR. TYNER: It's not bilayer. Thank you.

MS. DAVIDSON: And you mentioned a list of items early in your presentation that might not be liposomes, oil and water emulsions. Do you mind repeating those?

DR. TYNER: Looking at different formulations and how you can make them -- the typical inactive ingredients that are used to make the liposomes, if you don't form a liposome, you would typically form a solid lipid nanoparticle. You could form a micelle. You could form an oil/water emulsion. There are other structures as well, but those are the big ones. And those are not liposomes.

DR. GULUR: Dr. Hoag?

DR. HOAG: I have one clarification or question. Sometimes they'll make soft gel capsules, and they'll just be filled with oil. And in the capsule won't be any liposomes, but then

they kind of claim that once it's absorbed and it forms liposomes in the GI tract and then that facilitates absorption, are those included? Because there is some intent, but in the product itself there are no liposomes.

MS. BORMEL: I think that what we're concerned about is mainly compounding something that is a liposomal product. So it would be the product that's taken would have to be a liposomal product. I don't think the review has contemplated something that would be taken internally and then claimed to make liposomes in the body. We're just focused on the actual compounding of a liposomal drug product.

DR. HOAG: And would there be any restriction to the route of administration, getting back to the topical versus -- certainly with IV, there'd be I would think very big risks to compounding liposomes, but for a skin cream or cosmetic or something, would those still apply?

MS. BORMEL: We haven't restricted to any type of route of administration. What we're saying

is that all these products -- Dr. Tyner can correct me, but what we're saying is that liposomal drug products are difficult to make. They're difficult to compound.

DR. TYNER: So from a technical standpoint, just to follow up on that, all of the routes of administration are still going to fall under this technical difficulty for compounding. So the safety aspect of dose dumping clearly is going to be a risk to the patient for IV. It still can be a risk for dermal. Now, the risk-benefit ratio can be different, but that risk is still there.

DR. GULUR: Yes, Dr. Braunstein?

DR. BRAUNSTEIN: I think that the fact that something's hard to do shouldn't make it illegal because people can become technically proficient, but if the risk-benefit is going to be inappropriate, then we might regulate against it. I think that's generally the way the FDA regulates. I think we should keep that in mind. At least the voting members should keep that in mind when they consider the different types of products that one

might develop using this technology.

DR. GULUR: I guess I would like a clarification on that. I thought we were discussing difficult to compound products.

MS. BORMEL: Yes, we are discussing that, so the process would be -- there's a recommendation by the agency that liposomal drug products are difficult to compound, and then the committee will consider that and vote. And if it is determined to be difficult to compound, it would be put into regulation by a rulemaking.

So what we're saying is that these liposomal drug products are difficult to compound, and that's considering all the factors that Dr. Tyner has listed out above.

DR. BRAUNSTEIN: If I could just continue, there are a lot of things that were difficult at one time that are easy to do today. I think the point -- and this is at the end of Dr. Tyner's presentation -- was that because of the difficulty for these types of products, they felt that the risk-benefit would make these products fit the

definition of difficult to compound under the law because what we have to deal with is the way the law is written. You have to get into what was the intent -- we have to sort of read into what was the intent of Congress in writing that law.

Now, I'm not an expert in that, so I'm not going to perhaps get into that. Maybe the FDA might provide some more insight into that. But generally speaking, we don't prohibit doing something just because it's difficult, but because that difficulty then leads to some risk that we want to regulate against. That's generally the regulatory structure that we use in this country.

MS. BORMEL: That's correct. Even in the statute it says that it's demonstrably difficult to compound and it affects the safety and effectiveness of the product. And I think that's what Dr. Tyner was discussing at the end, dose dumping and things along those lines that would be a concern about the safety and effectiveness of the product as mentioned in the statute.

DR. GULUR: Thank you. We'll take one last

question from Dr. Wall on the phone on this.

DR. WALL: Yes, a quick question. What kind of adverse events have been reported [indiscernible] kind of technology?

DR. GULUR: What kind of adverse events have been reported?

Donna, did I get that right?

DR. WALL: Correct.

DR. GULUR: Dr. Rupp?

DR. RUPP: I can give you a little information. When we were looking at our adverse event database regarding adverse events related to compounded or what we would call liposome drug products, as you know, a lot of the drugs that are reported for adverse events do not have a lot of information, so it can be difficult to identify whether they really are liposome drug products or not. But we were able to identify a couple adverse event reports related to AmBisome that was reconstituted incorrectly.

MS. BORMEL: What is mandated or adverse reporting for FDA-approved products and also for

unapproved products. So we don't really see a lot of adverse events for compounded products unless it would come from an outsourcing facility.

DR. WALL: Okay. Thank you.

DR. GULUR: Yes, Dr. Davidson?

MS. DAVIDSON: And based on that, do you know what the universe is of compounders trying to prepare liposomal drug products, by this definition? Is it happening at all?

DR. RUPP: We weren't able to identify any that we think are actually making true liposomes with an API inside it, however, we do not know of the entire universe of what compounders are doing.

DR. GULUR: Dr. Mixon, would you like to comment on that?

MR. MIXON: Well, I don't have any more information on the universe of compounders. I would say on the 503A side, I can't imagine a compounder trying to do this. However, a 503B outsourcer operating under CGMP might find the need or the ability to do this, and I think that because the demonstrably difficult list applies to both, we

need to be very cognizant of that.

I'm still very concerned about the technical distinction between a liposomal drug delivery system and what we compound routinely when we use some of the products that we use on a daily basis like pluronic lecithin organogel drug delivery systems.

DR. GULUR: Thank you very much, Dr. Tyner.

DR. TYNER: Thank you.

Open Public Hearing

DR. GULUR: We do not have any nominator presentations for this. We will now proceed to hear open public hearing speakers. I'll read the following OPH statement into the record.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the

open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the product and, if known, its direct competitors. For example, this financial information may include the payment by a bulk drug supplier or compounding pharmacy of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics there will be a variety of opinions. One of

our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair. Thank you for your cooperation.

Please go ahead.

COL JOHNSON: Thank you, ma'am.

Well, just like yesterday, I'm still Colonel Jeff Johnson, Air Force retired. I am a consultant from MEDISCA, and MEDISCA is a compounding pharmacy support supply company. I did not share this yesterday, so I'll share it today.

I received my B.S. in pharmacy in 1978, 1978 not 1878. I do have a lot of gray hairs. I didn't see Lincoln get shot. I got my naturopath degree in 1999; my PharmD from University of Kansas in 2003. And again, I want to thank the PCAC, the chair, the FDA, our gallery, for this opportunity. I want to thank Dr. Tyner for her excellent presentation. I am a visual learner, so the pictogram on number 3 was very, very well done. I

want to also comment on something that Dr. Mixon commented on just a second ago, talking about innovation and also with our industry rep on difficult to do.

Being an Air Force veteran of 30 years, the Wright brothers over a hundred years ago were basically told we would never fly. And this is what the Wright brothers said to that.

"The desire to fly is an idea handed down to us by our ancestors who in their grueling travels across trackless lands and prehistoric times looked enviously on the birds soaring freely above them. If we worked on the assumption that what is accepted as true reality is true, then there would be little hope for advance." A hundred years ago, we couldn't fly; now we can. I think we need to keep that in mind.

We want to clarify exactly what's being considered today by using the label "liposome drug product" and by the description in the briefing document and what's been discussed. We are concerned that we are casting far too wide of a

net. The use of a liposome base, an inert vehicle used by compounding pharmacies today, combined with an API using mixing methods such as a mortar and pestle, ointment slab, or high-shear methods such an ENP machine, does not rise to the same level as what is to believed to be a concern.

We would encourage the PCAC to stress the need to separate those bases out from what's being considered. Further, we also believe there's a problem when you try to add a process and product to a demonstratably difficult list for both 503A and 503B pharmacies. 503A complies with USB; 503 complies with GMP standards.

We are very well aware that the Drug Quality Security Act passed by our Congress several years ago created the 503B or outsourcing facility. The statute requires then the 503Bs to register with the FDA and operate under GMP standards. Having the outsourcing facility adhere to GMP standards means they follow the same standards as our manufacturers, such as ADME that nominated that liposomes be placed upon this list.

Our point in bringing this up to you is to demonstrate that by placing this on the list, the FDA will be denying the outsourcing facility what was given to them by statute, the ability to produce a finished product. We are also concerned that by placing liposome drug products on this list, you will be stifling innovation.

We agree with the comments that were filed by the International Academy of Compounding Pharmacists, and as they do, we strongly encourage a limited and balanced approach when placing items upon this list. We do recognize and agree that some items placed upon the list previously do belong on that list. However, moving forward, it is necessary to review that these items have a concern being of impeding patient access to what could be a life-saving drug.

Given the rapid advancement of technology and the similar standards already being met by outsourcing facilities today, the only reason we think they can place liposome upon this list would be the unnecessarily protection of the financial

market for an already FDA reviewed drug.

I fully respect and understand the complexity of the creation of liposome drug products as described by Dr. Tyner, but nothing in the briefing documents or in the presentations today create a hurdle so high that it could not be met with the proper investment of time, money, and expertise by an outsourcing facility as technology develops. Thus, just as if a generic drug company's looking to invest into the continuation of a liposome drug product, and outsourcing facility has the same capability to follow the complex GMP rules laid out by the FDA just as that generic company does.

Let's remember that an outsourcing facility, a 503 compounding pharmacy, is there to fill a much needed gap such as the one we're currently experiencing and witnessing in Puerto Rico following the devastation experiences by the recent hurricanes. We are proud and fully support the FDA in their work of trying to get their program back up and running in Puerto Rico, but it is very

important to remember we need to keep as many possibilities open for outsourcing facilities, 503Bs, to help these patients access, not hinder their access, needed pharmaceuticals and health care. We fully and support recommending not adding liposome drug products to the demonstrably difficult list.

That concludes my statement, ma'am.

DR. GULUR: Thank you.

Any questions for our public hearing speaker? Sir, are you aware of any 503B facilities that are currently manufacturing under this?

COL JOHNSON: No, ma'am.

Committee Discussion and Vote

DR. GULUR: Thank you.

The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. We will now begin the panel discussion of liposome drug products. Dr. Mixon?

DR. MIXON: I think the question of whether there are any 503B outsourcers attempting to make

liposomal products is best addressed to the FDA because outsourcers are required to report what they make.

DR. GULUR: Is the FDA aware?

MS. BORMEL: We're not aware of any outsourcers producing liposome drug products.

DR. GULUR: Dr. Vaida?

DR. VAIDA: How would these products even be prescribed, like for a 503B to even make them? It would be either a current product that's approved, which they can't make unless there's a shortage, or they would have to come up with a new product that they would actually advertise? I'm just missing that point with the 503Bs with this dosage form.

MS. BORMEL: The 503Bs, they can either compound something that's in shortage. The bulk drug has to be a component of something that's in shortage, or the bulk drug has to be on a list that's in the FRN, and there's a guidance on that right now. There's no list. So basically what they'd have to do, I believe, is they would have an order to -- if they were doing something liposomal,

they'd have to use a bulk that's on a list and figure out some sort of liposomal formulation for it. There's no list. There's guidance with an interim policy. That's where the 503B bulks interim policy is.

DR. GULUR: Dr. Carome?

DR. CAROME: Mike Carome. I'll note that if you look at the FDA's records, which they make publicly available on inspections of outsourcing facilities -- and the majority I think have been inspected -- the vast majority of inspected facilities have received a 483 form, which documents often a lengthy list of serious violations of good manufacturing practices, and many of those have gone on to get a warning letter. So I would have little confidence in an outsourcing facility's ability to make a liposomal product.

DR. GULUR: Dr. Davidson?

MS. DAVIDSON: I still need clarification on how FDA would determine that a liposomal drug product compound has been compounded. Would you determine that by labeling, by claim? Would it be

perhaps in response to a reported adverse event? I still wonder how you would detect this if it were happening.

MS. BORMEL: Well, the easiest thing is to have a labeled claim that a product is a liposomal formulation because that means the compounder intends it to be a liposome and deliver it in that way. The FDA in general, in response to adverse events, has gone into different compounders and done inspections or investigations, depending on the adverse event. So we may become involved that way, too, and then analyze the product.

MS. DAVIDSON: So if I've made one of these topical preparations that uses a penetration enhancer, and I accidentally form liposomes and don't even know it, am I at risk? That is my big concern here, is that we may doing something that falls into this very large bucket of liposome drug products and not even know that we're doing that.

MS. BORMEL: The way the consult's written, it would cover bulks that are intended to be delivered, APIs that are intended to be delivered

in the liposomal formulation. So if you're using the cream and you add -- you're using a penetrating cream as a base and you add bulk product to it, and you just say this is -- or API to it that is a component of an FDA-approved product, or subject to a USP monograph, or on the bulks list, and you just say this is XYZ cream, and you make no claims that it's liposomal, that's not what's covered by this review.

DR. GULUR: Dr. Bogner?

DR. BOGNER: I have a question about the public speaker's contention that 503Bs are covered by GMP. But since these are not new drugs, does the same testing occur

DR. AGARABI: I can speak to that. I think that there is a little bit of confusion about CGMPs or 503Bs versus a conventional manufacturer. There is a statement that the 211s apply here, and actually we've been tasked with creating 213. And 213 is CGMPs for outsourcer facilities, and we've taken a look at those specific needs of outsource facilities and not holding them to the same

standard as a traditional manufacturer.

I think this also ties into the other point about if they follow a GMP, can't they just make this? We go through that exercise when we consider the science here and we consider the risk. And if you follow the GMPs, we still have concerns about testing that is more than the norm. So a standard applicant product will do a PK study. They'll do bioavailability studies. They'll use that information to set specifications.

I would defer to our industry representative to ask him how important development in early clinical trials is when setting your process. And that's not just following GMP for doing a test. We consider the totality of the package when we get a submission. For 503B firms, they play a really important role, and we want them to be able to perform under CGMPs that are appropriate, but there are still products, or types of products, that may be too difficult to compound in the 503B or 503A realm that are better suited for the 211 world.

Hopefully that helps to clarify. 211 world,

for those who are not familiar, is what we call what a conventional manufacturer would follow. And they would have rigorous testing that is reviewed by the FDA, and they go through many rounds of submissions so that we are on the same page about the testing requirements and development requirements.

DR. GULUR: Thank you. Dr. Braunstein?

DR. BRAUNSTEIN: So I think I'm also getting a better understanding of what the FDA is seeking to put on the list because it has to do with the word "intention." You would only intend to create a liposomal drug delivery system if you're intending that that liposomal system, because it's a complex system -- the only reason you would go to the trouble to do that is because you wanted to do something special with that drug, either to protect it from degrading -- that might be one reason -- or to deliver it to a particular site, which is a more typical reason.

Well, if that's the case, and was just discussed, in order to understand whether or not

your liposomal drug delivery system is achieving the goal that you are seeking to achieve, you would need to do clinical studies, most likely. So now we're getting out of the world of GMPs and just do -- even if you had a sophisticated facility that also did QC testing and was able to do these complex analyses of liposomes, that could be done. Somebody could buy the equipment; learn the technique.

That's conceivable. Right? It's physicochemistry. But when you get to the step of now having to do clinical studies, now we're getting into what manufacturers do. Actually, I don't think you would then call that a 503B pharmacy; you would then call that a manufacturer.

Maybe the FDA can expound on this. It really has to do with the intention to create a product that has the need for a liposomal delivery system to achieve the purposes that one would normally create a liposomal drug delivery system to have, like a delivery to a specific site.

Is that what this is about because that

would make --

MS. BORMEL: Yes, that's correct. You can be CGMP compliant and just as you said, you can make this product, but that may not -- make a product that doesn't dose dump, for example; you would never know that just from the CGMP aspect alone.

DR. GULUR: Any other questions or clarifications? You do have one.

DR. BOGNER: I have a few more.

DR. GULUR: Yes. Go ahead, Dr. Bogner.

DR. BOGNER: Thank you. When we say difficult to compound, who are we talking about? Is this a quote/unquote "person" of ordinary skill in the art; an average pharmacist with no additional training? Is this somebody who retires from a major pharmaceutical manufacturer in formulation and processing and goes to work for a 503B or opens a compounding pharmacy? How do we imagine this person?

MS. BORMEL: The statute in both 503A and 503B have provisions on difficult to compound. So

when we're putting forth this list, the intent is that it's difficult to compound for both a state-licensed pharmacy under 503A and also an outsourcing facility under 503B.

DR. GULUR: Dr. Carome?

DR. CAROME: But just to follow up, if it's not on the Difficult to Compound List, then any compounder, 503A or 503B, could compound one of these drugs.

MS. BORMEL: Correct.

DR. GULUR: Thank you. Yes, Dr. Hoag?

DR. HOAG: I was just going to say, one thing I think is what's needed to make these products safe, especially for IV, is the testing regime. And unfortunately, the state of science today is not developed that if I just had a formulation a priori, I could test it and say that's how it would perform in the patient.

That's where this is going back to clinical studies and stuff because, unfortunately, I could measure particle size, but is that really going to be how it performs in the body? Unfortunately,

that would be an area of research that needs to be developed more before you can say, all right, I have XYZ specifications for this formulation; I can say it's safe. Unfortunately, that's not the state of science.

DR. GULUR: Thank you. We will now end our discussions and start the vote. The question before us is FDA is proposing that liposome drug products be included on the Difficult to Compound List under Sections 503A and 503B of the FD&C Act. Should liposome drug products be placed on the list?

The panel will be using an electronic voting system for this meeting. Each voting member has three voting buttons on your microphone: yes, no, and abstain. Please vote by pressing firmly your selection. After everyone has voted, the vote will be complete.

Voting will be on the drug product just presented. After the completion of the vote, we will read the vote from the screen into the record and then hear individual comments from each member.

If you vote yes, you are recommending placing these drug products on the Difficult to Compound List under Sections 503A and 503B of the FD&C Act. If a drug product is included on this list, it cannot be compounded in accordance with Sections 503A and 503B.

If there is no further discussion, we will now begin the voting process. Please press the button on your microphone that corresponds to your vote. You will have approximately 15 seconds to vote. After you have made your selection, the light will continue to flash. If you are unsure of your vote, please press the corresponding button again.

(Voting.)

DR. CHEE: For liposomes, we have 9 yeses, 1 no, and zero abstain.

DR. GULUR: We will begin with comments. And this morning, since it's a new morning, Dr. Carome will help us.

DR. CAROME: I voted no. I think FDA laid out a clear and compelling case for why these drug

products are demonstrably difficult to compound. And on the six factors in terms of complexity of formulation, drug delivery, mechanism, dosage forms, characterization, and controlled bioavailability, the compounding process and the analytical testing required on each of those, the case is compelling that this is difficult to compound.

I think there's great potential for doing harm to patients if these products are made incorrectly, and for those reasons, I voted no. I voted yes

DR. GULUR: For the record, Dr. Carome, you voted yes?

(Dr. Carome nods in the affirmative.)

DR. GULUR: Dr. Hoag?

DR. HOAG: I voted yes. I would like to add a couple caveats. One is for IV, I certainly think this is appropriate. If it's a topical preparation, an oral preparation, or cosmetic or something, maybe it's not. The risk to the patient is not there. Also, I don't really understand the

capabilities of these compounding facilities and things, so I can see under appropriate conditions if they did have those capabilities, which I'm not really sure one way or the other if they have that, that that would be -- if they had suitable testing regimes, that that would be appropriate.

Also, I think in the future, I could see someone coming up with a platform technology that may make safe liposomes. I don't know of anything that exists, but I think this needs to be reviewed as technology advances to keep current.

MS. JUNGMAN: Elizabeth Jungman. I voted yes because I found the FDA's presentation to be compelling both in the complexity of making these products and also the difficulty in doing backend testing to make sure you got what you thought you got.

DR. BOGNER: Robin Bogner. I voted yes, based on the current technology, but I would like to reaffirm Steve Hoag's comment that as there is progress in the field of technology advances to remove this from the list, I think that should be

considered.

DR. PATEL: Kuldip Patel. I voted yes primarily because of the lack of technology available to do media testing to obtain PK/PD data. I wasn't so much concerned about the discussion about complexity because I do believe that compounders can overcome the complexity. They're doing it now like the general pointed out with the drug shortages in Puerto Rico and compounding complex things like amino acids. So I go with a yes.

DR. GULUR: Thank you. Dr. Wall on the phone? Dr. Wall?

(No response.)

DR. GULUR: We'll continue for now. Dr. Humphrey?

MR. HUMPHREY: William Humphrey. I voted yes. I was convinced by the FDA's presentation and some of the comments from colleagues.

DR. GULUR: Dr. Davidson?

MS. DAVIDSON: Gigi Davidson. I voted yes for many of the reasons that have been stated,

again with caveats that intent is applied to any regulatory decisions around a compounder who is preparing a liposome drug product, and also that, again, this question comes up over and over again, will the list, can the list be reviewed in a continuous process as technology changes and compounders may someday have the ability to safely and accurately compound these dosage forms.

DR. GULUR: Padma Gulur. I voted yes for reasons already stated by others and appreciate the caveats that my colleagues have made as well.

Dr. Vaida?

DR. VAIDA: Allen Vaida. I voted yes for the reasons that have already been stated. And also, I feel that even with advanced technology, if you're going to compound a drug like this, you would still have to test it in clinical trials; otherwise, you'd be compounding a drug that already exists, and that's not allowed unless it's on a shortage.

DR. GULUR: Dr. Wall, are you available on the phone?

DR. WALL: Yes, I'm on the phone now. Sorry about that. I hit the wrong button. I voted no, even though I had some really grave concerns about it being used especially in IV formulations. But if I had a choice, I would really like to say tabled [indiscernible] because I think you presented a good picture, but I think it needs more definition, especially when you look at the topical compared to some of the others. And we may be using too broad of a stroke with this.

I do think there needs to be additional testing when you do get into these complex forms, but I would just hate to shut out something really beneficial in an effort to get rid of some of the things that are more dangerous. Thank you.

DR. GULUR: Thank you, Dr. Wall.

With that, the vote is concluded. We will take a break at this time. If everyone could return to their seats by 10 a.m.

(Whereupon, at 9:48 a.m., a recess was taken.)

DR. GULUR: Welcome back, everyone. We will

now proceed with the FDA presentation on drug products produced using hot melt extrusion by Dr. Cruz.

FDA Presentation - Celia Cruz

DR. CRUZ: Good morning. My name is Celia Cruz. I am currently in the Office of Testing and Research within the Office of Pharmaceutical Quality. I am a division director in the Division of Product Quality Research. I'm actually a chemical engineer by training. My PhD is in chemical engineering. I worked in industry for about 11 years and have firsthand experience with this process of hot melt extrusion.

I've been at FDA for about seven years. We also have hot melt extrusion technology in our labs, and we actively do research on this. We actually have firsthand experience with a lot of the analytical methods that we're going to be discussing today used to characterize these formulations. With me today is my colleague, Dr. Naresh Pavurala, who will also be available for questions in the question and answer portion.

In this presentation, much like the previous one, we will give the background on what is hot melt extrusion, and we will go through the evaluation criteria to discuss how considering whether these formulations are recommended to be part of the Difficult to Compound List. We will discuss the risk and benefits to patients and formulate a recommendation.

So what is hot melt extrusion? For the purposes of this presentation and as part of our review in the consult, FDA defines HME as a continuous process operation that achieves, or is intended to achieve, the molecular mixing of active pharmaceuticals, or APIs, and inactive ingredients, most likely a polymer, and we will discuss this in detail, at temperatures above their glass transition, temperature and/or melting temperature, within the extruder.

Why would people apply hot melt extrusion? It's actually a pharmaceutical manufacturing process that's gaining in popularity, and the objective of this process is to enhance the

solubility of poorly water-soluble drugs by converting the formulation components to a single amorphous phase, meaning non-crystalline, product. This product is referred to as the extrudate.

In this pictorial, we show how you can feed an API independently with its own properties as well as additional inactive ingredients when you feed the mixture into the hot melt extrusion process, which we'll be discussing in detail. It transforms the materials from crystalline into amorphous, into a single-phase solid, and this material can then be processed further for additional dosing.

We will probably come back to this slide a few times in the discussion. Basically, an extruder is shown here, the principle components of it. Extrusion has some general characteristics in terms that there is feeding of API and inactive ingredients into the extruder.

The extruder has a twin screw or can be sometimes a single screw assembly, and these turn at a given speed. Everything is housed within a

barrel, which actually can have a temperature profile, which is set along the length of the screws. The material can be fed at a certain rate, and then it is conveyed. And with this addition of heat and shear, it is converted to a single-phase, melted material, which then exits through the die, and then it's quickly cooled upon exit.

In general, we'll speak of feeding, conveying of this mass, flow through the die, and further processing. For the scope of this review, we are considering hot melt extrusion, the process, from feeding of the API and inactive materials up to the formation of this extrudate.

These steps can be summarized in feeding a mixture of API and inactive ingredient, the selection, and the operation of barrel, screws, and transport through the section, which will then simultaneously mix, heat, and convey the material; the application of heat and shear to these materials to force them through this orifice, and the cooling portion of the extrudate to form a material that can then be further processed into a

finished dosage form.

The temperature profile within the extruder barrel, the screw configuration, which we'll be discussing in detail, and the speeds are optimized to maintain proper conveying and mixing without thermally degrading the material, which will then cause impurities in the material.

We will discuss how hot melt extrusion has specialized raw material selections and control, is a distinctive manufacturing process, and has unique in-process and final control measures, which all contribute to quality of the product. That would be to ensure the API solubility and enhance bioavailability to ensure product safety and efficacy through this measure and also to ensure minimal impurities due to preventing degradation within the extrusion process.

As part of our difficult compound analysis, the evaluation criteria considered in formulating a recommendation as to whether or not products using HME have demonstrable difficulties for compounding are as follows. We'll go through complex

formulation, complex drug delivery mechanism, complex dosage form, characterization and control bioavailability, the compounding process, and physicochemical or analytical testing, and we will discuss the complexities in each step.

The first one is to talk about the concepts of complex formulations. Most importantly, we will discuss the properties of the API and the inactive ingredients and how they can impact product quality. Selection of API and inactive ingredient is difficult due to the limitations on API and inactive ingredients that will result in a stable amorphous phase when extruded. Basically, not any API and any polymer, and not any combination of those two, will result in an acceptable extrudate.

The critical quality attributes of the extrudate, or how it's intended, is a single amorphous phase, which is uniform, performs adequately, and is stable in the drug product. To maintain the quality of the drug products produced using HME, the extrudate must maintain its form, meaning it should not be crystallized after

production, during storage, and upon release in vivo. Therefore, the formulation selection is difficult, as components should be carefully chosen to ensure that this extrudate has these critical quality attributes.

If we start with the API, we have to think of the fact that the thermal properties of these APIs have to be very well understood. The HME process conditions require that the API be thermally stable and maintain its chemical stability through the process entering storage. A failure to understand the limitations of API performance under temperature and shear could lead to improper extrusion conditions, generation of impurities, and lack of compatibility of the API and inactive ingredients in the process.

The melting point of the API and where the material actually starts degrading thermally has to be well understood and has to be well within the ranges of the process. As noted above, we are converting the API and the polymer into an amorphous phase, but it's well known that an

amorphous phase can be less thermodynamically stable than the crystalline state.

Since we want to maintain bioavailability to increase the solubility of these poorly soluble APIS, understanding that tendency to remain as an amorphous is very important. Therefore it is essential to monitor the glass transition temperature of the extrudate containing the API under various conditions and humidity conditions because, actually, these could accelerate the recrystallization process.

Not only do you have to understand the thermal properties of the API, but there are two kinds of solubility that are important here. The first is the API solubility in water because you need to understand the change in solubility between crystalline and amorphous phase, which would have a direct impact on bioavailability. It's been quoted in the literature that this can be twofold for up to several orders of magnitude that changes solubility.

The solubility of the API and the polymer

are also important, and this is solid in solid solubility. A lot of this requires formulation work in terms of understanding the composition of the system and whether or not it is likely to stay in a single phase.

The solubility of the API and the polymer is increased as the temperature's increased through the melting process. Partially miscible components may lead to a solid particulate dispersion system, which is not the desired quality. Where the API is only partly dispersed or potentially crystalline may have consequences in terms of extrudate quality, and a physical mixture of the API and polymer may exist, which is not the desired state.

Therefore, establishing the solubility limit, or what is known as the maximum API to polymer ratio, is really important in understanding the formulation and the complexities of these formulations. This requires pre-formulation work of physical characterization of the ingredients independently and together and is critical for achieving proper product performance.

If you think of the API in itself, but it's being converted in the HME process, it can actually come in different crystalline forms. Crystallinity of the API can be different and have different melting points, different tendencies to change, and can actually impact a product differently, so understanding the crystalline state of all incoming materials is very important. Some APIs may also exhibit thermally induced polymorphism and actually could have negative implications in terms of resulting in crystalline API through the extrusion process if the conditions are not carefully selected.

Then we have to think of the concepts of API purity. With the hot melt extrusion process, it's not only important to understand the degradants that are in the API or the potentially processed impurities that are in the API as it comes in, but actually the level of solvent is very important. Either water or other solvents that are in the API are removed through the HME process, therefore degradants may increase during the heating process

and potentially impact safety if they're not carefully controlled, and interactions between API and other impurities that may be coming in, whether residual solvents or thermal impurities, during melting and quenching should be analyzed through accelerated stability studies and is typically done to understand the potential of the HME to convert phases.

If you think of the components in the extrudate, the API is obviously very important because it is the drug, but the API carrier, which is mostly polymeric is a very important selection factor. Drugs produced via HME contain API embedded in this carrier as the final system, so these polymers can function as thermal binders, drug stabilizers, drug solubilizers, and depending on the properties of the polymer can actually have drug releasing controlling mechanisms. They're mostly polymeric, though they can be non-polymeric in some instances.

The polymer should exhibit appropriate thermoplastic characteristics, meaning as the

polymer heats up, it should flow in the correct way so that it can be well processed but also be able to release the drug when necessary. The carrier should be able to be processed at relatively lower temperatures to make sure the heat-sensitive APIs are protective.

Selecting a polymer with inadequate thermoplastic characteristics can result in a non-uniform extrudate phase, and the potential for crystallinity and degraded API may increase if this selection is not done correctly.

There are many kinds of inactive ingredients that could go into hot melt extrusion formulation, so we talked about obviously the polymer, and we'll talk about one more that's actually very important. It's the concept of plasticizers. Since you're actually melting and flowing viscous materials through the extruder, plasticizers are typically low molecular weight compounds that are used to soften the polymers and to make them more pliable, which actually enhances the HME process.

Plasticizers are often used with polymer

carriers and HME and improve the condition during processing and a lot of times improve the actual physical and mechanical properties of the final product. But if selected into the wrong amounts or types can actually be detrimental to the final product.

They have to be appropriately selected and controlled during the process. If improperly selected, the lack of API release from the extrudate can happen. The temperature requirements may be wrong, and you may have inadequate viscous flow during the extrusion process. Most commonly used plasticizers include citrate esters, fatty acid esters, sebacate esters, phthalate esters, glycol derivatives such as polyethylene glycol and propylene glycol.

There are many other inactive ingredients that could be added to this formulation adding to its complexity. And even though they would have a particular role in the extrusion process, they also have to meet the thermal and thermoplastic requirements of the process. These can be

antioxidants in case the API is prone to oxidation or maybe the polymer is. Light absorbers can also be used to improve stability of the polymers that are prone to degradation at high temperatures. Some commonly used antioxidants are listed here.

Other inactive ingredients that can be added that add the flow into the system for example can be silicon dioxide or other lubricants such as glyceryl monostearate, which help improve the mixture through the extruder. These ingredients must be properly selected and characterized and controlled in consideration of the desired characteristic of the resultant formulation.

In terms of the complex formulation, extrudate must remain as a stable and amorphous solid solution of API within a matrix. This needs to happen at the time of extrusion and throughout the shelf life so that the final product can have a proper performance.

Extrudate should have uniformed distribution of API in the matrix and a controlled level of impurities. It is critical for the formulation

components -- both API and inactive ingredients of which we talked about, polymer for example and solubilizers, along with others -- to be thermally stable during the extrusion process and for the formulation to be physically stable afterwards.

Selection and control of raw materials in ratios that are appropriate for the extrusion and for the future stability of the extrudate is very important. Therefore, drug products produced using HME have a complex formulation and present demonstrable difficulties for compounding.

We'll now talk a little bit about complex drug delivery mechanisms. If you go back to the concept of the extrudate, the extrudate formulation determines the solubility and dissolution of the API from the matrix. And as we discussed, the choice of the polymer, the inclusion of plasticizers, the inclusion of solubilizers can have a lot in terms of the release of the product.

The drug delivery mechanism should ensure that the API does not recrystallize in situ. In addition to that, when the extrudate is added into

the final dosage form, this can depend on the design of that dosage form. The type of extrudate matrix and the amorphous state of API can then be modulated and controlled within that dosage form, and there are many examples of dosage forms that utilize extrudate.

The extrudate can be employed with products that microencapsulate, have target delivery, mask taste, film coat, and modify release, and also use nanotechnology. The qualitative and quantitative characteristics of API and inactive ingredient, the physical design of that dosage form, and the site of action all influence the release rate and intended performance of drug products using HME.

The mechanism by which API is released from the drug products produced by HME can be complex because it depends on the product design, and these can be immediate or sustained. That implicates API dissolution has to be correct and the solubility and the amorphous state has to be maintained to ensure appropriate drug delivery.

This product design involves achieving and

maintaining this amorphous state, the correct selection of the API in terms of the ratio with polymer, and to understand the intended release conditions. Precise control of raw materials and the extrusion process are necessary in order to achieve and ensure safety and efficacy. The complexity of drug delivery mechanisms of drug products produced using HME present demonstrable difficulties for compounding.

Let's talk about dosage forms. You just had a little bit of a discussion on that. Some dosage forms of drug products produced using hot melt extrusion are complex because of the structural arrangement or distribution of the extrudate within that dosage form. The functional role of the extrudate in the dosage form's drug delivery mechanism can be really important and add to the complexity, but also the interaction of extrudate with other ingredients within the dosage form.

We can come up with many examples to illustrate this in terms of whether you have modified release, or depending on the dosage forms

in which the extrudate, which contains the API and the polymer that releases it, are incorporated into that dosage form. For example, for a topical drug product produced using HME, such as an ointment, and we've discussed ointments today, it is critical to appropriately process the extrudate in order to yield a particular viscosity in the final dosage form, a drug release profile that enables either local or systemic drug delivery, depending on the intent, and a texture of firmness that is compatible with an ointment.

Similarly, if a topical film drug product is produced via HME, the extrudate needs to be produced in a way that provides the proper interaction with the inactive ingredients so that the product adheres to the skin and delivers the API appropriately. The same can be said with complex tablets or other types of dosage forms.

Extrudate can be incorporated into different dosage forms and for different routes of administration for a given therapy to increase bioavailability and product performance. In most

dosage forms, the extrudate in other ingredients may need to be of a certain size and shape within the dosage form and arranged in a particular way to deliver the API properly. This is done through downstream processing after extrudate cooling.

Drug products produced using HME require well designed controls of ingredient attributes and process parameters for predictable API release from that dosage form. This requires extensive product development work and precise control over raw materials selection,, and the production processes are essential to evaluate the API release mechanism and desired profile and other product performance characteristics. Ultimately, if the extrudate fails to deliver that drug at the correct rate or with the correct solubility, it can be directly impactful to that drug delivery mechanism and the dosage form.

As we discussed, one of the main goals of products produced via hot melt extrusion is to increase bioavailability, and it's mostly applied to low solubility drugs or what's called poor

solubility compounds. FDA defines bioavailability as the rate and extent to which the active ingredient is absorbed from a drug product and becomes available at the site of action.

Due to the increased solubility of API following extrusion, minor variations in the formulation in the extrudate can significantly impact bioavailability and in turn the safety and effectiveness of a product. Formulation and production process of drug products produced via HME need to be well controlled to achieve a specified measure of API solubility at an optimal rate and extent of API absorption at the site of action.

It is critical to measure the impact of recrystallization on bioavailability, which is done in vivo and utilized by relevant dissolution media to predict performance, which can be done in vitro to ensure that products have a consistent release rate of API that falls uniformly within predetermined and specific acceptable ranges. This connection between the testing that needs to be

done to ensure bioavailability, based on the properties of that extrudate and how it was made versus what is needed in terms of ensured bioavailability, is very critical.

Characterizing and controlling the bioavailability of drug products produced using HME can be complex. Subtle changes to any components or production process could significantly impact a drug product's solubility and intrinsic dissolution, which in turn can influence local and systemic bioavailability. In most of the cases, why these formulations have been designed this way and this process has been selected is to improve bioavailability.

For drug products produced using HME, in vitro assessments such as dissolution testing, alone are not generally sufficient to accurately predict bioavailability and overall clinical effect; rather, in vivo assessments are needed. Therefore, characterizing and controlling bioavailability of products produced using HME is complex and presents a demonstrable difficulty for

compounding.

So if you go back to our depiction of a hot melt extruder, we can talk a little bit about the complexity of the compounding process. If we think of the parameters that need to be controlled in this process, we already talked about the different properties of the materials, we need to control the feeding rate of the material because then it will impact the fill of this extruder, which would then impact the amount of energy in the extruder due to shear and mixing.

This concept of the screw profile, it is configurable. As you see, you have different types of flight distances, and you can actually select what kind of extruder configuration you want. The more mixing elements you have, the more energy this continuous extruder could impart on the material, which could lead to degradation in higher temperatures but perhaps better mixing. Then if you have less mixing elements, the material would just convey. So the point is that this screw is configurable and needs to be determined.

In addition, we have these barrel sections, which can be heated, and the temperature set points on all these can be independently controlled, the speed of this screw as well as the quenching and cooling conditions.

As we discussed, there are several parameters here that are important. Controls are necessary before, during, and after the HME process to ensure that the extrudate achieves and maintains CQAs of amorphous state, uniformity, and purity. Typically, a central electronic control unit used in the HME processing controls the various process parameters as set. This could be screw speed, feed rate, temperatures along the barrel and the die, and the vacuum level, and the vacuum level to remove solvents from the system that may be coming in with the materials.

Extruders allow in-process monitoring and control of certain parameters as well as monitoring of others. For example, barrel temperature, feed rate, and screw speed are controlled and need to be set based on the properties of the materials we

have already discussed, while motor load and melt pressure are monitored. And these are measured responses and need to be within certain ranges to know that the process is continuously making good product.

If you think of just the screw profile and the screw speed, the main assembly of the extruder consists of a motor and a gravimetric feeder, which drives the material through. The drive motor controls the screw speed while the gravimetric feeder controls the feed rate. So you can actually move the screws that are given speed and feed the material at a given rate, and these are independent of each other. However, the screw speed and the feed rate, even though they're independent, they need to be predetermined and specific depending on the characteristics of the ingredients going into the extruder.

Variations in the combination of screw speed and feed rate may affect what's called the residence time, which is how long the material spends in the extruder, and the mixture going

through there and being exposed to melt pressure, shear rates, and temperature, and how high the temperature of the material will achieve. If these variables fall outside the predetermined parameters, the extruder may not exhibit the desired characteristics, meaning too low, you might end up with non-amorphous extrudate, too high, and you might end up with degraded API.

The concept of temperature is also independently controlled. In this extruder system and in all extruder systems, temperature and heat, basically heat rise, are generated in two ways, either in the extruder due to frictional heating within the barrel caused by the shearing of materials between the rotating screws and between the screws and the wall.

Basically, the material friction generates mechanical energy, and it can heat the materials as well as the heat in the barrels, which are controlled by heating elements that are mounted externally to the extruder. You can also have the profile have cooling sections in the beginning and

heating at the end in order to maintain a consistent profile as desired.

Temperature controls are necessary at all times to maintain the melt viscosity and allow for proper conveying and mixing without thermally degrading the ingredients. Selecting the appropriate temperature profile, meaning it's not just one temperature along the extruder, is important and will lead to robust conveying and processing.

Once the extrudate is actually coming out of the die in its melted form, it needs to be cooled. Most desirable is to cool it rapidly so that the properties of that extrudate are quote/unquote "frozen into place." Once the extrudate exits the barrel through the orifice, it must be cooled at this rate that is predetermined.

The cooled extrudate at this point is a glass, or an amorphous solid, which can then be processed downstream through conventional pharmaceutical equipment like milling, cutting, blending, compressing, encapsulation, among others.

Basically, the form of the final dosage form is established then. Variations in barrel temperature, extrudate cooling rates, and endpoints may alter the characteristics of that material.

As we have spoken, HME requires specialized equipment under appropriate controls and is critical to ensuring quality. The extruder must be properly calibrated based on the properties of the ingredients fed into the extruder and the desired characteristics of the extrudate.

As we discussed, by properly calibrated, we're talking about a multivariate system. We need to consider the screw profile, the screw speed, the feeding rates, and the temperature profile along the barrel. Poor technique or control at any step will likely result in a product that does not achieve or maintain critical quality attributes.

For example, it could lead to an unstable, non-uniform, crystalline extrudate, which may result in diminished API bioavailability, and in turn may adversely affect the safety and effectiveness of the drug product. Therefore, HME

is a complex compounding process that presents demonstrable difficulties for compounding.

We've now moved on to the concept of testing. We talked a lot already about the types of properties that are necessary to be controlled for incoming raw materials, the product itself as it's being manufactured, and also product quality through storage.

In terms of raw material testing, rigorous characterization of the ingredients processed by HME is important to avoid negative impact on safety and efficacy because of how these materials will process. Raw material properties such as melt viscosity, the thermal properties we've discussed, and impurity content can often have negative impact and need to be understood.

FDA is not aware of available standards for raw material testing, for example found in USP, that capture these specific aspects of melting and crystallinity. To conduct complex methods of testing for raw materials, using HME is critical for the processability of the components,

understanding them as individual materials, as well as the mixture.

Once the extrudate is done, a measurement system that properly characterizes the extrudate is complex because it incorporates multiple complementary methods to interpret similar properties. This is the concept of crystallinity. It's not usually done just by one method and needs complementary methods to really understand the state of the material and its propensity to recrystallize.

Properly determining the extrudate quality is not always possible through the interpretation of a single analytical technique. A critical quality attribute of the extrudate being in an amorphous state inside the carrier matrix requires analytical methods that are needed to detect whether there is a single glass transition temperature for the extrudate confirming to that criteria.

For example, you might be using multiple methods to understand the quality of the extrudate.

That could be microscopy to understand particle size and crystallinity and detect the presence of drug crystals or air bubbles within the extrudate; application of x-ray powder diffraction and spectroscopy to again understand crystallinity as well as composition being correct; and concepts such as non-sink dissolution to understand the drug release performance and stability of that extrudate in terms of delivering the drug; and obviously, the workhorse for HME, thermal analysis; so typically, not only differential scanning calorimetry but modulated differential scanning calorimetry to understand the difference between glass transition temperature measurements and whether or not there's the presence of crystalline material in the extrudate.

It is very important to not only understand it in the final state of the extrudate, but also its relationship with temperature and uptake of moisture because it's really relevant in terms of storage of these materials.

Other techniques can be thermomechanical

analyzer, which tell you, as the increase in temperature, what the type of viscous properties and pliability of these materials will be; thermogravimetric analysis, which will tell you about the loss of solvents and also concepts such as water uptake; and obviously high performance liquid chromatography to understand purity and assay for the related drug substance and the related substances; and also to check any chemical degradation of known thermal impurities.

The concept of stability for an extrudate is not something that happens in a long three-year time period. Recrystallization can actually occur quickly depending on the moisture uptake and the temperature to which the material is exposed. It can also be done incorrectly if it's not processed right.

Actually, monitoring of the quality of the extrudate through the shelf life included at the moment of manufacture or processing as well as storage is very important. It is one of the major challenges because the concepts of testing

crystallinity, as we just saw, requires several analytical techniques.

Typically, stability of the extrudate in the final product should be evaluated during initial stages of product development and to understand the recrystallization potential of an API within an extrudate is very important. Extrudate in the final dosage form also needs to be evaluated because the combination with other inactive ingredients after processing needs to be understood, and usually the techniques for this include accelerated, stressed, or long-term stability studies.

The concept of hygroscopicity of the extrudate can be quite significant because polymers can be hygroscopic, which reduces the glass transition temperature of the extrudate and promotes recrystallization. Once this material is made, keeping it with the correct uniformity and form is very critical.

Hot melt extrusion being a continued operation, to understand whether you're making an

extrudate that is of the right composition and of the right form a lot of times requires in-process measurements. These can be in the form of novel analytical techniques such as in-process controls.

Sometimes PAT has been readily applied, and near infrared and Raman spectroscopy can be used to monitor and control the HME process, which gives you the right composition of API and other ingredients, as well as the solid state forming. This is very important because you can understand whether the extrudate is actually being formed in the correct quality.

If you look at the complexity of the measurement system from the raw materials, the in-process controls, and the final drug product, physicochemical and analytical testing performed before, during, and after the HME process to evaluate thermal properties, recrystallization potential, and dissolution and uniformity requires specialized analytical devices and procedures for accurate measurement, and therefore are complex and present demonstrable difficulties for compounding.

As we talked about this, this technique is used to increase the solubility of poorly soluble drugs. Drug products produced via HME can benefit patients due to this enhanced bioavailability. They also produce solid materials, which can be stored and handled more easily. They can provide controlled delivery rates and these concepts of stabilized formulations. Compounded drugs however are not FDA approved, but they can serve an important role for patients whose clinical needs cannot be met by an FDA-approved drug.

Currently, the agency is not aware of any human drug compounds that produce drug products using HME. Such products could potentially benefit patients if they are produced with taste-masking properties suitable for children or in dosage forms that are suitable for patients with difficulty swallowing such as mini tablets or liquid suspensions. We also talked about different examples for ointments, et cetera.

While the compounding of drug products using HME would pose a significant risk to patients, HME

process design complexities and the relationships between inactive ingredient and API products produced via HME can directly impact bioavailability, the release, and performance of the product. These in turn affect drug product effectiveness and safety.

If erroneously substituting or removing inactive ingredients such as the polymer, plasticizer, or surfactants, it could lightly change the solubility and the release characteristics of the product, and in turn may adversely affect product performance.

Consistent quality controls for raw materials and the extrusion process and final product all need to be in place and are essential for predictable and reproducible API release, which then in turn can affect safety and effectiveness. Therefore, any potential benefit of compounded drugs produced via HME could be outweighed by the risks.

We have evaluated the category of drug products produced using HME as a candidate for the

Difficult to Compound List. Based on an analysis of the evaluation criteria presented today, we believe that the drug products produced using HME present demonstrable difficulties for compounding that recently demonstrate or are reasonably likely to lead to an adverse effect on the safety or effectiveness of such products.

Taking into account the risks and benefits to patients, we believe the products produced using HME should be included in the Difficult to Compound List under Sections 503A and 503B of the FD&C Act.

Clarifying Questions from the Committee

DR. GULUR: Thank you. We will accept clarifying questions at this point. Dr. Vaida?

DR. VAIDA: It looks like the API is really important in this. Is there just certain APIs, certain products that could even qualify for this?

DR. CRUZ: Right. The good candidates typically used for APIs need some help with solubility. But in terms of selecting an API that could be suitable for this type of process, it has to have -- they'd be called low melters, or if they

have a high melting point, they might need the help from a plasticizer or solubilizer to melt at a lower temperature.

Not only that, after melting, the threshold for degradation for the high temperature can be right away. So you need some space between melting and degradation. Therefore, understanding the thermal properties of the API and selecting those APIs that can be used in this type of process is very important.

DR. VAIDA: Once a drug is approved, like when the FDA approves a drug by this process, then other manufacturers have to follow that? I'm looking at the list that the nominator sent of their drugs, so something like levothyroxine. They have Synthroid down, but all the generic levothyroxines now follow this process?

DR. CRUZ: Generics of solid oral dosage forms are not required to use the same process necessarily that an innovator does. They need to meet the same critical quality attributes.

DR. VAIDA: Okay.

DR. GULUR: Dr. Carome?

DR. CAROME: For the traditional drug manufacturers that use these types of formulations in this manufacturing process, what type of review does the FDA do to ensure the quality of the process for the end products?

DR. CRUZ: We pay close attention to the development of the process in terms of the multivariate attributes and process parameters that are needed to achieve the extrudate quality. We pay close attention to the definition of what is extrudate quality; for example, fully amorphous and the measurement systems that are used to determine whether or not the material is fully amorphous.

Also, there is the formulation development section that talks about biopharm effects and bioavailability in terms of formulation selection, meaning how important is the crystallization in the amorphous part in terms of bioavailability for that product. So the dissolution folks spend a lot of time looking at that as well.

DR. CAROME: And are there examples where

the FDA during that review process has found problems and directed the manufacturer to make changes because of the review?

DR. CRUZ: We will be very diligent in terms of asking them to develop methods that can ensure the quality of the product. And also obviously through inspection, we would look at whether or not they are looking at all the controls that are necessary for the process. But essentially, we need to be able to detect the concept of recrystallization if those are important for the bioavailability of the product.

DR. GULUR: Dr. Bogner?

DR. BOGNER: Thank you. That was a nice review of hot melt extrusion. Thank you.

DR. CRUZ: Thank you.

DR. BOGNER: If somebody wants to compound with a small twin-screw hot melt extruder --

DR. GULUR: Dr. Bogner, would you lift the microphone up? Thank you.

DR. BOGNER: So if somebody wants to compound something with a twin-screw hot melt

extruder, not necessarily to make it amorphous but to maybe due a traditional -- the old kind of solid dispersion a la Sakaguchi and Obi, the old paper from way back when, that would not be covered under this because there's no intention to make it amorphous?

DR. CRUZ: We believe it would still be covered because you still need to know what your target is in that situation. For example, any consideration in terms of targeting a particular property like 8 percent of some sort of amorphous conversion, that would need to be qualified and understood in terms of the properties of the product. The probability using the compounding, the selection of the materials, and the testing of that could still be demonstrable -- it could be still difficult to compound to still achieve those targets.

So the use of an extruder as a mixing device is not what is talked about here. In all these cases, the materials, through the heating and shearing, experience a phase transition that needs

to be well qualified and understood in terms of the quality and the product.

DR. BOGNER: So if somebody simply wants to create, as I said, a traditional non-amorphous dispersion just so that the polymer fully wets and you've got compression and densification, that would not be covered under the current discussion. They could do that because they're not seeking an amorphous --

DR. CRUZ: So our review focused on the amorphous part. Our concern with applying it to that would be you would be using a tool that may impart some issues in terms of degradation if you are exposing it to heating, if you're trying to do something like granulation perhaps, maybe where there's a better tool to do that in that case. But I don't know if policy has anything else to add.

DR. BOGNER: I guess my concern is that we raise temperature a lot when we make suppositories.

DR. CRUZ: Right.

DR. BOGNER: There are a number of times in compounding we raise temperature, and that's not

the issue. We're talking about the amorphous piece that's the big issue.

DR. CRUZ: Amorphous piece via hot melt extrusion. So if it's using an extruder under the conditions we have described and the materials have experienced this transition into an amorphous phase, it ideally it's going fully amorphous, but one of the concerns is if the target is different than fully amorphous, it may be hard to control it anyway.

DR. BOGNER: I understand.

DR. CRUZ: So it's as described in this.

DR. BOGNER: But hot melt granulation then is still on the table.

DR. CRUZ: Yes. Hot melt granulation is not part of this scope.

DR. BOGNER: Thank you.

DR. GULUR: Any further clarifying questions? Dr. Vaida?

DR. VAIDA: Is this process common among manufacturers? Do a lot of manufacturer have this -- I mean, obviously, the nominator has like

19 drugs and IV. Do other manufacturers have this? You said you didn't find any in the compounding.

DR. CRUZ: Right. So in terms of manufacturers, there's the nominator list. Also you could do literature searches. For example, we quoted in our review a list by Stankovic, et al. published in 2015, obviously not fully comprehensive, but there you have a list of about 13 products with different dosage forms that are used with hot melt extrusion.

It's obviously not as common as granulation or something simpler, but in terms of increasing the solubility of APIs that fit the profile in terms of not thermally degrading, it is growing in terms of its use, but it's not as common as your typical granulation type of processes. I don't know if you're looking for a number or --

DR. GULUR: Dr. Davidson?

MS. DAVIDSON: Thank you for a really comprehensive presentation. The ingredients, both active and the excipients, would seem to me -- and I know I'm really oversimplifying this -- to have

known physical constants that could be accessed and applied thoughtfully to the process. The trick it seems to me comes in analytical testing to determine the bioavailability and the performance of the finished extrudate.

You made a statement that you can't rely on in vitro testing; particularly for the bioavailability that has to be in vivo. Can you help me understand that a little bit more maybe from the perspective of what manufacturers do?

DR. CRUZ: Those are concepts of what is a discriminating in vitro method that's telling you whether quality has been impacted that is relevant to the clinic. For example, if you have an amorphous extrudate and the solubility of the API and the extrudate has been improved by this amorphous state, if you have a 10 percent recrystallization, 25 percent, 50 percent, at some point bioavailability will be impacted.

So you need an in vitro method for dissolution as well as for detecting the presence of crystals, and then understanding whether that

impacts dissolution and release rate that are somehow connected to in vivo trials that tell you, yes, at 20 percent recrystallization, this product is no longer bioavailable.

So those connections actually are done, and just in vitro doesn't tell you the answer. It's the connection between the two that is most powerful.

MS. DAVIDSON: Do you think it's possible that in the future, if not now -- I don't know -- that a contract laboratory could perform this sort of in vitro testing to give back some knowledge about performance of the extrudate?

DR. CRUZ: The connection of in vitro and in vivo would have to be there still. So in vitro, you might have a dissolution method that might be developed with different levels of recrystallization, but you might not know when product failure is identified based on the in vivo performance. So that still would need to be answered.

MS. DAVIDSON: One more question if you'll

indulge me. Do manufacturers do that with -- how do they make that connection? Do they do that with laboratory animals first, or do they jump right to humans? I'm not figuring out how you get to that point.

DR. CRUZ: Both.

Open Public Hearing

DR. GULUR: If there are no further questions, thank you, Dr. Cruz.

We do not have any nominator presentations. We will now proceed to hear open public hearing speakers. Do we have any open public hearing speakers?

Please introduce yourself.

MR. DePASQUALE: Hello, committee member and esteemed colleagues. Thank you for the opportunity to speak. Sorry for my voice. I lost it.

My name is Seth DePasquale. I'm a pharmacist and co-owner of BET Pharm. BET is a small compounding pharmacy located in Lexington, Kentucky, dedicated to providing innovative quality compounds for the equine industry. I tend to

describe our company as a niche within a niche, within a niche. We're a compounding pharmacy that not only compounds sterile injectable medications for horses, but we tend to focus primarily on equine reproduction, as my partners have a combined experience of over 70 years in that business.

We're also fortunate to have had a formulation scientist, a chemist, that was known or who actually came up with all the formulations that we make today. He had spent most of his career at the Southern Research Institute in Alabama. We have a small portfolio of compounds, but the need for what we make is there given this small number of manufacturers that are interested in this very limited size market, particularly for horses.

I'm here to speak specifically about hot melt extrusion today. To give a little background, we use an extruder to make two compounds, but our most popular is one allows a horse owner to give a single-dose injection once every 30 days to suppress estrus in a mare. The alternative is a commercially available medication that is given

orally and is typically sprayed under the horse's feet or directly into their mouth.

Just to be clear, this is a progestin, a hormone which obviously disrupts the reproductive cycle of the horse, but it also can have effects on the human administering the medication as well, and oftentimes it is being administered by a young female of reproductive age. Our product is not only slightly more user friendly, but is a much safer product from this standpoint. I should also mention that the two formulations that I'm referring to are both commercially available products, and BET's compound use the same active pharmaceutical ingredient.

First, I truly don't intend to derail this conversation, but I do have one point of clarification I really feel needs to be discussed. In the FDA's review of drug products produced through the hot melt extrusion process, it is defined as a continuous process. This does not have to be performed as a continuous process. It could actually be done in batches. I'm not trying

to split hairs, but perhaps that should be clarified as we actually do this in batch form rather than as a continuous process.

I'd like to briefly mention some of the research that we conducted and published in the Journal of Equine Veterinary Science showing the effectiveness of our alternatives compound with an endpoint of delayed estrus and onset of ovulation post-menstruation of our formulation.

Looking at these endpoints of days to estrus and days to ovulation, we show that estrus is successfully suppressed for a period of 32 to 34 days. The data consistently shows that this compound is not only effective but dependable in suppressing estrus in a manner that has been repeated month after month, year after year, for the past eight years, since we began compounding this formulation.

As a compounding pharmacy, we maintain records of any complaints or adverse events on any of our compounds, and I pulled the records from the last two years and have a reported adverse reaction

rate of less than 1 percent, a total of 6 reactions, all being injection-site reactions, which is a known reaction given the polylax [indiscernible] polymer we use. By our own standard operating procedure, we perform sterility and endotoxin testing per USP 71 and 85, respectively on all of our compounds, including our extrusion products.

Given that this is an intramuscular injection, we also perform potency testing on every other batch. We consistently see that from a potency standpoint of our final compound, it is always within specification of plus or minus 10 percent using a third-party lab that analyzes our compounds' potency using the HPLC.

When it isn't, we have procedures in place to identify when there's an issue and reject the batch prior to any of those doses leaving the pharmacy. However, since we perform this process the same way every time using the same material, getting both API and polymer from the same manufacturers every time, we honestly don't see

much variability from batch to batch. I'd also like to mention that this compound is terminally sterilized via gamma radiation.

There are certainly critical process parameters that must be carefully accounted for during the production. The briefing document describes some of those really well, including melt temperature, melt pressure of the rotation speed of the screw, and various temperatures at different points in the barrel of the extruder. All these must remain consistent throughout the entire process in order to produce a compound that's going to exhibit the same outcome in the patient every single time.

All this being said, I just have a couple points of contention. First -- and I've already stated this in my submission on regulations.gov, but it's worth repeating -- the level of complexity is dictated by the persons formulating and manipulating the compound. The level of complexity itself is self-limiting.

Our particular product is fairly simple in

that there are only two ingredients in the HME process, and it's a single pass through one extruder. Of course, there are other products that may use a combination of multiple extruders to form layers of certain ratios of API to polymer mixtures over top another layer that may have a slightly different ratio of API to polymer in order to release the drug over a specific time period, or to reach a particular target, or to delay the release of the drug. This again would be self-limiting given the possible need for multiple extruders or extremely precise machinery in order to accomplish this procedure.

The briefing document also points to the fact that hot melt extrusion doesn't lend itself to be a process for every API. Only certain APIs will be able to withstand the temperatures required so as not to completely degrade and destroy the drug rendering it useless. This perhaps could be overcome with the addition of plasticizers, but again you would need to do quite a bit of discovery and research to figure this out, another

self-limiting factor given that not every API could be used, which leads to my final point.

Many of the evaluation criteria identified for this particular process does describe some critical process parameters but mostly, with the briefing document, describes other critical quality attributes that need to be defined during the process, development, and design of the formulation itself.

What I'm driving at here is, is the demonstrably difficult list trying to include the production process of hot melt extrusion? Given the examples of the evaluation criteria, it seems more like what is being claimed is that it's too difficult to even formulate a compound that may use hot melt extrusion for production.

Specifically, it cites limitations of selecting APIs to various chemical thermal and physical properties of excipients, the stability of the extrudate. These are parameters that need to be examined not during the production process necessarily but in the research and development of

a compound.

I honestly think the question that's being put before the committee today is whether the FDA should allow pharmacies and pharmacists, or companies that serve as pharmacies, to research and develop compounds that would be processed using hot melt extrusion. I would submit that if a pharmacy is given the burden of proof to provide evidence that they have done the research and development, and have considered and account for the critical quality attributes and critical process parameters, why wouldn't they be able to compound using hot melt extrusion?

Thank you very much for your time, and I hope everyone has a happy Thanksgiving.

Committee Discussion and Vote

DR. GULUR: Thank you.

We will now consider the open public hearing portion of this meeting concluded and no longer take comments from the audience. We will begin the panel discussion.

(No response.)

DR. GULUR: We will now end our discussions I guess. Yes, Dr. Jungman?

MS. JUNGMAN: Would it be the IND process that a pharmacy or another facility would use to demonstrate that they had the capability to do this, or is there another mechanism for taking advantage of that suggestion?

MS. BORMEL: In order to show that the product is doing what it said it would do, it would have to go through the NDA process. As we heard, in vivo requirements are necessary with the HME process in order to show that it has the effect that's intended.

MS. JUNGMAN: I think the suggestion was that there should be some room to continue to experiment and explore, and it seems to me that a vote here -- and I think this is really more a principle for us moving forward -- isn't a vote that you can't continue to work with these products. Right? It's just you would do it under an IND as opposed to doing it under compounding. Correct?

MS. BORMEL: Yes. You'd have to go through the process.

MS. JUNGMAN: Can I just ask one more question? I just want to clarify, we're only voting with respect to human use of this process. Right?

MS. BORMEL: That's correct. That's what we're dealing with.

DR. GULUR: Yes, Dr. Davidson?

MS. DAVIDSON: In that light, I just heard Dr. DePasquale describe that he does this in batches in veterinary, so it's okay. But it seems to me, again, that 503B facilities might be very capable of using this technology, but any decision here today would preclude them from doing that as well.

MS. BORMEL: Yes. If something is put on the Difficult to Compound List, it would apply to both 503A state-licensed pharmacies and 503B outsourcing facilities. I think that Dr. Cruz had mentioned that it's not only important how the product is made, but also with respect to

bioavailability, the in vivo data is very important.

MS. DAVIDSON: I would like to point out or maybe discuss that bioavailability and safety and efficacy -- maybe safety but not efficacy -- have never been in the realm of compounding; that is in the practice of medicine. A compound is usually for one-off patients. So if this technology were used for one patient and tested with all of the appropriate in vitro mechanisms, would it still not be able to be evaluated by the prescriber for that individual patient as a compound?

MS. BORMEL: Well, what the statute says when we put something on the DTC list is that it's demonstrably difficult to compound so as to affect the safety or effectiveness. So in this particular case, what you're referring to would adversely affect the effectiveness.

MS. DAVIDSON: One more question. I think I heard that any use of this particular piece of equipment would be considered difficult to compound by this application.

MS. BORMEL: No. I think what we -- I'm going to defer to Dr. Cruz, but I think it's the HME process.

MS. DAVIDSON: I wanted to tie in to what Dr. Bogner was saying. I was a little confused there about where the scope of this decision will be.

DR. CRUZ: Hot melt extruder is a unit operation. The operation itself is continuous. It doesn't mean that the entire process -- you can make batches of extrudate, but the unit operation itself is continuous. It's continuous flowing through the screws.

So in this scope, the operation or the process is defined as feeding through the extruder, the heating section, and the extrudate coming out of the die. That's where it's at. For example, if there's downstream processing that's separate, it's this particular unit operation, you could call it, that is under consideration with that scope of the process and the materials involved.

MS. DAVIDSON: So if the same process were

used to mask taste or other applications, it would not be considered -- I'm still really confused about --

DR. CRUZ: If you're still using the hot melt extruder, even if you were saying I'm using it just to mask taste, you could still have the risk to quality on the product because of the difficulty in selecting the materials, the equipment operation, the measurement systems to show that you did not adversely affect the product. So for this particular unit operation which could impart those risks, we believe that in this scope, it would be covered.

MS. DAVIDSON: I think not the nominator but the presenter submitted some information on 3D printing. Where does that fall into this discussion? Is that a completely separate issue or would this one-time decision affect any potential use of hot melt extrusion in that capacity? Because it sort of is hot melt, maybe not extrusion, but hot melt. And again, I'm way out of my wheelhouse even trying to talk about this.

Then related to that, what is the precedent for making this decision today for humans in terms of compounding for animals, which I'm aware of more than one application for this technology in animal use.

DR. CRUZ: I'll answer the 3D printing part. 3D printing itself is the definition of additive manufacturing, and it can be done through many different mechanisms. It's the composition of layers, one on top of another, through a predefined structure of some sort.

Hot melt extrusion per se is not linked to 3D printing. There are 3D printing mechanisms that use powders with binders. There can be fused filaments, which is maybe what they're leading to here, but hot melt extrusion wouldn't preclude future discussions on 3D printing, which is additive manufacturing itself. So far, the technology for additive manufacturing has an incoming material that's already preformulated and then is layered based on some sort of program. So this concept of continuously doing hot melt

extrusion is not necessarily linked to the additive manufacturing piece at this point.

MS. DAVIDSON: Okay.

DR. GULUR: Yes, Dr. Bogner?

DR. BOGNER: He was going to answer the veterinary --

DR. GULUR: Oh. Please go ahead.

DR. GHOBRIAL: Just to remind folks, these provisions, difficult to compound provisions, are written into Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act, and they don't relate to animal drug compounding.

For questions on how compounded drugs or the activities here may affect future animal drug policy, we would ask you to submit those to the Center for Veterinary Medicine at cvm@fda.hhs.gov. We do know that they're actively looking at their policies, not in this space related to difficult to compound, but others.

DR. GULUR: Yes, Dr. Bogner?

DR. BOGNER: The issue has been raised in vitro to in vivo correlation for products made from

this particular process. But how different is that from other products that are approved by FDA? Is it more so, more true of HME products?

DR. CRUZ: I think what we try to talk about here is the difficulty in making the connection, meaning it has to be actively evaluated through multiple methods in order to make the distinction between whether bioavailability has been impacted or not. For example, there might be some considerations in terms of the propensity of that API to recrystallize, the conditions that would be more prone to make that happen, and then the sort of level of detection you would need to understand whether that formulation has reached a point where it's no longer bioavailable.

So those questions, probably the cost to bioavailability is asked of every product, but the complexity here is the connection of how you made that extrudate, the materials you used to make it; the in vitro characterization to detect crystallization or amorphous state, and then the propensity for that to change upon storage. And in

proper conditions, it can happen within a week. So these are the kinds of things that the connection between these three are usually addressed through development.

DR. BOGNER: If I may continue, it's my experience that even a small amount of crystal in the solid dispersion would reduce bioavailability. That's why I asked the question that if you were not intending to make this fully amorphous, or even largely amorphous, are we still talking about that. And I would like to think that those processes might be considered separately.

I would like to make the observation that this is a pretty fast-moving field. And I know you're aware of this, but there are platforms out there -- we have Soluplus -- so there are graft copolymers that are being made to enable this technology to be more successful. And there are also drugs out there that are very difficult to recrystallize, so there are some that you can't get them to recrystallize.

So this is not an every time difficult to

compound. Largely it may be, but since it's such a fast-moving field with platforms coming out, I am not sure that it's worth making a decision today. But that's just my comment, and I look forward to a response.

DR. AGARABI: So just to dovetail on the point about applying the standard of in vivo versus in vitro and why wouldn't we always apply that standard -- and we can point to the last 20 years the work we've done with the biopharmaceutical classification system, and the agency has put out numerous guidances on biowaivers. So if you have a high solubility/high permeability drug, you don't necessarily need to do the same level. The question was, would a sponsor have to always do a clinical trial, and the answer may be biowaiver.

So I think it's really important when we talk about HMEs, which are low solubility types of products that are self-selected in because they're difficult to solubilize, that the level of getting it approved now is still very high and requires in vitro and in vivo testing.

DR. GULUR: Any further questions?

(No response.)

DR. GULUR: We will now end our discussions and start the vote. The question before us, FDA is proposing that drug products produced using hot melt extrusion be included on the Difficult to Compound List under Sections 503A and 503B of the FD&C Act.

Should drug products produced using hot melt extrusion be placed on the list? If you vote yes, you are recommending placing these drug products on the Difficult to Compound List under Sections 503A and 503B of the FD&C Act. If a product is included on this list, it cannot be compounded in accordance with Sections 503A and 503B.

If there is no further discussion, we will now begin the voting process. Please press the button on your microphone that corresponds to your vote. You will have approximately 15 seconds to vote. After you have made your vote selection, the light will continue to flash. If you are unsure of your vote, please press the corresponding button

again.

(Voting.)

DR. CHEE: For hot melt extrusion, we have 7 yeses, 2 nos, and 1 abstain.

DR. GULUR: Dr. Vaida?

DR. VAIDA: I voted yes, going with the recommendations of the FDA and based also on currently. I believe currently it's difficult to process, it's difficult to identify the API, and currently you do need in vivo testing.

DR. GULUR: Padma Gulur. I voted yes for reasons already stated, the difficulty in testing and requirements around that, and the current technology influenced my vote.

MS. DAVIDSON: Gigi Davidson. I voted no because I believe the technology has clearly advanced on the veterinary side. I appreciate the complexities that were presented in the presentation, but I do believe that to prohibit all hot melt extrusion compounding right now is a premature decision. And if I had my wish, I would delay this decision, but right now I vote no.

MR. HUMPHREY: William Humphrey. I voted yes, similar to the other yes votes. I do think technology will catch up with this, though.

DR. PATEL: Kuldip Patel. I voted yes. I do agree with some of the comments made earlier by Dr. Bogner and Dr. Davidson's comments. My primary reason behind voting yes was the issue with bioavailability and the lack of data in vivo, however, I think more obviously needs to be done to research it under the proper guidance to make the technology successfully usable in the compounding world.

DR. GULUR: Dr. Wall on the phone?

DR. WALL: My technology was messing up, so I missed a good part of the conversation and didn't feel it would be appropriate to vote.

DR. GULUR: Dr. Bogner?

DR. BOGNER: Robin Bogner. I voted no because this is a fast-moving field. I don't know that there are examples of HME being used for human drug compounding, so I don't know what we're solving by putting it on the list. More

importantly, I don't know how to get items off the list, so I'm very concerned about prematurely putting them on the list.

MS. JUNGMAN: Elizabeth Jungman. I voted yes. While it would depend on the particular API at issue, I think FDA made the case that this is a process that would be better suited to a pre-approval framework because the need for product development work and control over raw materials selection and process is to ensure a predictable API release and characteristics, and really means that for any particular application, it would make sense to see evaluation prior to exposing patients to the product when using this technology.

DR. HOAG: Steve Hoag. I voted yes. This was tougher than the last one because I do feel it's a fast-moving field, and at some point, it may be appropriate. I guess the main reason that I voted that it be included is because currently you have to do some development work. All these stability problems don't always show up right away, so you need to have long-term. We've done studies

where it would be precipitated two months later, and I don't think compounders do that type of thing, so that was part of it.

Also, in terms of the veterinary field, that was a different example. That was like a controlled release device, so it shows the versatility of this. I don't eat horse, but I would worry about if it was food animals, are these getting good reliable release rates because I wouldn't want to consume progesterone or some of those compounds that could be potentially put in food substances.

DR. CAROME: Mike Carome. I voted yes. Again, I thought the FDA made a compelling case that this is demonstrably difficult to compound. In particular, I think it's important that there be in vivo clinical testing in humans before these products are used in patients. I think the pathway to changing the list -- I think they're two pathways. The FDA could revisit the issue at some point if technology changes significantly and ask the committee whether the list should be changed,

and anyone could submit a citizen's petition asking for a change to the list.

DR. GULUR: Thank you, Dr. Carome.

With that, this session is concluded. If the FDA officials would like to make some closing comments.

MS. BORMEL: Again, I'd like to thank the committee members for their time and for the review of the materials. And we wish you all a Happy Thanksgiving.

Adjournment

DR. GULUR: Thank you. Happy Thanksgiving to everyone.

(Whereupon, at 11:19 a.m., the meeting was adjourned.)