FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACY COMPOUNDING ADVISORY COMMITTEE (PCAC)

Wednesday, June 17, 2015

Morning Session

8:32 a.m. to 11:30 a.m.

FDA White Oak Campus

10903 New Hampshire Avenue

Building 31 Conference Center

The Great Room (Rm. 1503)

Silver Spring, Maryland

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P R O C E E D I N G S

(8:32 a.m.)

Call to Order

Introduction of Committee

DR. VENITZ: Good morning, everyone. I would first like to remind everybody present to please silence your cell phones, Blackberrys, 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. Can you please raise your hand? Right there in the back. Please stand and everybody knows who you are. Thank you.

Good morning. Again, my name is Jurgen Venitz. I'm the chair of the Pharmacy Compounding Advisory Committee, otherwise referred to as PCAC. I would now call the committee to order.

We will now ask those at the table, including the FDA staff and committee members, to introduce themselves starting with the FDA to my left and moving along to the right side, ending

with one of the industry representatives, Mr. Ned Braunstein.

Let's start off on our left. Would you please introduce yourself?

DR. ROBIE SUH: Kathy Robie Suh, clinical team leader, Division of Hematology Products, CDER.

MS. ZIOLKOWSKI: Olivia Ziolkowski, Office of Regulatory Policy, CDER.

MS. AXELRAD: Jane Axelrad. I'm the associate director for policy in the Center for Drug Evaluation and Research and the agency lead on compounding.

MS. BORMEL: I'm Gail Bormel. I'm the acting director for the Office of Unapproved Drugs and Labeling Compliance within the Office of Compliance.

MR. HUMPHREY: I'm William Humphrey. I'm the director of pharmacy at St. Jude Children's Research Hospital in Memphis.

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

DR. WALL: Donna Wall, member of Indiana

Board of Pharmacy, and I'm a clinical pharmacist. I'm here representing NABP.

DR. VAIDA: Allen Vaida. I'm a pharmacist, and I work at the Institute for Safe Medication Practices.

MS. PETERSON: Good morning. I'm Jayne Peterson. I'm the designated federal officer for the Pharmacy Compounding Advisory Committee.

DR. VENITZ: Jurgen Venitz. I'm a clinical pharmacologist and professor at the VCU School of Pharmacy.

MS. DAVIDSON: Gigi Davidson. I'm the chair of the USP Compounding Expert Committee, and I'm representing USP.

DR. GULUR: I'm Padma Gulur. I'm a professor of anesthesiology and pain medicine at the University of California Irvine.

DR. DiGIOVANNA: I'm John DiGiovanna. I'm a dermatologist in the dermatology branch at the National Cancer Institute.

DR. PHAM: Katherine Pham, NICU clinical specialist at Children's National Medical Center.

DR. CAROME: Mike Carome, director of Public Citizen's Health Research Group, and I'm the consumer representative.

MR. MIXON: Good morning. Bill Mixon. I own The Compounding Pharmacy in Hickory, North Carolina. I'm also a member of the North Carolina Board of Pharmacy and the USP Compounding Expert Committee.

DR. BRAUNSTEIN: Good morning. I'm Ned Braunstein. I'm a rheumatologist and a cellular immunologist. I'm the industry rep for the pharmaceutical industry. My day job, I'm head of regulatory affairs at Regeneron Pharmaceuticals.

DR. VENITZ: Thank you, everyone, for introducing themselves.

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 issues 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 the 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.

Over the next two days, we will cover three topics. On the morning of the first day, we will consider drug products proposed for inclusion on the list of drugs that have been withdrawn or removed from the market because they have been found to be unsafe or ineffective.

During Session 1, we will hear presentations from the FDA, ask clarifying questions, hold an open public hearing, and then have committee discussion and voting.

This afternoon, we will hear presentations from FDA and from nominators regarding four bulk substances nominated for inclusions on the list of bulk drug substances that can be used in compounding under Section 503A.

Additionally, we will hold an open public hearing and have committee discussion and voting on each of the four substances.

Let us begin. We will now have Ms. Jayne Peterson read the conflict of interest statement. Ms. Peterson?

Conflict of Interest Statement

MS. PETERSON: 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 Boards 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 government 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 federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members of this committee are in compliance with the federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular government employees who have potential financial conflicts when it is determined that the agency's need for the special government employee's services outweigh 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 meetings, members of this committee have been screened for potential financial conflicts of interests of their own as well as those imputed to them, including those of their spouses or minor children, and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts; grants; CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

During this morning's session, the committee will receive updates on certain issues to follow up on discussions from the last meeting, including the options for obtaining access to investigational new drugs and the processes FDA plans to use to add or remove drugs from Section 503A, bulk drug substances list.

During this session, the committee will also

discuss revisions FDA is considering to the list of drug products that may not compounded under the exemptions provided by the FD&C Act because the drug products have been withdrawn or removed from the market because such drug products or components of such drugs have been found to be unsafe or not effective. The list of those drugs products is currently codified at 21 CFR 216.24.

FDA now is considering whether to amend the rule to add four more drugs to the list: aprotinin, ondansetron hydrochloride, bromocriptine mesylate, and acetaminophen.

As previously explained in the Federal Register of July 2, 2014, the list may specify that a drug may not be compounded in any form or, alternatively, may expressly exclude a particular formulation, indication, dosage form, or route of administration from an entry on the list because an approved drug containing the same active ingredients has not been withdrawn or removed from the market.

Moreover, a drug may be listed only with

regard to certain formulations, indications, routes of administration, or dosage forms because it has been found to be unsafe or not effective in those particular formulations, indications, routes of administrations, or dosage form. FDA plans to seek the committee's advice concerning the inclusion of these drug products.

This is a particular matters meetings during which specific matters related to the four products will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members, no conflict of interest waivers have been issued in connection with this meeting.

Drs. Humphrey and Vaida have been recused from participating in the discussions and voting for bromocriptine mesylate.

To ensure transparency, we encourage all standing members to disclose any public statements that they may have made concerning the products at issue.

We would like to note that Dr. Donna Wall is a representative member from the National

Association of Boards of Pharmacy and Ms. Gigi Davidson is a representative for 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 as standing members representatives from the NABP and 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 a voice of the NABP and USP, entities with a financial or other stake 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 the owner of The Compounding Pharmacy.

We would like to remind members that if the discussions involve any other products 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 with the products at issue.

Thank you.

DR. VENITZ: Thank you, Ms. Peterson. Before we proceed, let me introduce our member that got stuck in traffic. Dr. Jungman, can you please introduce yourself briefly?

MS. JUNGMAN: Sure. I'm Elizabeth Jungman. I direct public health programs at The Pew

Charitable Trust.

DR. VENITZ: Thank you. Let's now proceed with the FDA introductory remarks from Ms. Jane Axelrad, the associate director for policy in the Center of Drug Evaluation and Research and the agency lead on compounding.

I would like to remind public observers at this meeting that while the meeting is open for public observation, public attendees may not participate except at the specific request of the committee. Thank you.

FDA Introductory Remarks - Jane Axelrad

MS. AXELRAD: Thank you, and good morning. I'd like to welcome you to the second meeting this year of the Pharmacy Compounding Advisory Committee, and I want to thank the members of the committee for their willingness to serve on the committee and to Dr. Venitz for being willing to chair the committee. We really appreciate the time that you take to do this, and we really value your participation and hearing your views about the topics that we're going to be discussing.

At the first meeting of this committee on February 23rd and 24th, we begin our work on developing the list of drugs that may not be compounded under the exemptions provided by Sections 503A and 503B because they or their components have been withdrawn or removed from the market because they've been found to be unsafe or not effective.

At the last meeting of the committee, you voted on 25 products that FDA proposed to add to the list that's already codified in our regulations at 21 CFR Section 216.24. You also voted on a proposal to modify the description of one product, bromfenac, to add an exception for ophthalmic use. In addition, you voted on whether to modify the listed entry for adenosine to clarify what products are covered by that entry.

At the last meeting, we also began our work to develop the list of bulk drug substances that can be used in compounding by entities seeking to qualify for the exemptions under Section 503A. You discussed and voted on six substances that have

been nominated for that list that FDA had evaluated.

During the last meeting, as you were considering individual drugs, committee members asked a number of questions about whether drugs that were placed on the withdrawn or removed list, or drug substances that were not placed on the 503A bulk drug substances list, would be available for patients. And we said that an expanded access investigational new drug application would be the mechanism to make such drugs available.

We provided some information about the expanded access mechanism on the spot. As you recall, somebody who was here got up and talked a little bit about it, but we thought that you might benefit from a more formal presentation.

So today, Dr. Jeff Murray will present information about the expanded access mechanism and how it could be used to provide access to products that will not be able to be compounded and still qualify for the exemptions under Section 503A.

After Dr. Murray's presentation, we're going

to continue our work on the withdrawn and remove list, and Gail Bormel will present information about the process we're using to identify and evaluate candidates for that list. She will also introduce the four additional drugs that we're going to discuss at the meeting, and then you'll hear presentations from the review divisions about the individual drugs.

This afternoon, we'll turn again to the list of bulk drug substances that can be used in compounding under Section 503A. I'm going to give a little presentation that describes, in more detail, the process that we're using to evaluate candidates for that list, how we're establishing priorities for those reviews, and how we plan to manage the list once they are developed. Again, this came out of questions that arose at the last meeting, so we're going to try and address some of that.

After that, we'll present the results of our reviews on four additional nominated substances for your consideration, and then you'll have the

opportunity to hear from the nominators of those substances.

Tomorrow, we're going to turn to a completely new topic for the committee, drugs that are difficult to compound and should not be compounded under either Section 503A or Section 503B.

One of the conditions under Section 503A is that to qualify for the exemptions under that provision, a compounder cannot compound a drug product that is identified by FDA by regulation as a drug product that presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product.

That is a mouthful, and you'll be hearing me repeat something like that several times over the next day or two. Section 503B also refers to a list of difficult-to-compound drugs.

Tomorrow morning, I'm going to describe in more detail the statutory framework and the history that we have of developing a list of drugs that are

difficult to compound under 503A. It's a fairly short history, but we do have some history on that. I'll also talk about the statutory provisions on difficult-to-compound drugs under Section 503B, which, of course, wasn't enacted until November of 2013.

Then we're going to present for your consideration and discussion the criteria that we're proposing to use to evaluate drugs and categories of drugs that may be considered difficult-to-compound under either Section 503A or Section 503B.

We have a very full agenda for the next day and a half, and we're really looking forward to the productive discussions that we expect to have and to hearing your views on the very important questions that we're going to be bringing to the committee over the next two days. Thank you.

DR. VENITZ: Thank you, Ms. Axelrad.

We will now proceed with the FDA presentation from Dr. Jeffrey Murray, deputy director in the Division of Antiviral Products. He

will speak on the expanded access to investigational drugs for treatment use.

Dr. Murray?

Presentation - Jeffrey Murray

DR. MURRAY: Good morning. I'm Jeff Murray from the Division of Antiviral Products, and I'm here to give you more details on expanded access processes and mechanisms, and our division of antivirals have seen a lot of expanded access over the years.

Expanded access is always carried out under an investigational new drug application or IND regulations. This is a safeguard for patients. One only needs to recall that FDA's role on the regulation of novel medicines was borne early out of tragedy when 71 adults and 34 children died in 1937 from taking an elixir of sulfanilamide. IND applications allow FDA to review information on investigational new drug products before they are administered to humans to prevent disasters that occurred back in 1937.

IND submissions, investigator

responsibilities are key parts of the regulatory requirements to protect patient safety under an IND, and it allows for some FDA review of chemistry, manufacturing, and animal toxicology studies, perhaps literature or articles before drugs are administered. There's also an investigational review board requirement and review, and then there's informed consent from the patient.

What is the definition of expanded access? A lot of people call this compassionate use, but expanded access is now, I think, the preferred term. Expanded access is treatment access to an investigational drug, including a biologic, outside of a clinical trial setting but under an IND for patients with serious, life-threatening diseases or conditions when there is no comparable or satisfactory alternative.

What is a serious condition? This is also in the regulations. It's a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and

self-limiting morbidity is usually not considered sufficient but morbidity need not be irreversible if it is persistent or recurrent.

Now, whether a disease or condition is serious is a matter of clinical judgment, and it's based on the impact of such factors as survival, day-to-day functioning, or the likelihood that the disease, if untreated, will progress to a more severe condition or a serious one. So there's a lot of flexibility in this definition, and it's clinically-based.

What is some general information on expanded access? Well, it facilitates availability of investigational for drugs, as I stated, for patients with a serious or life-threatening disease as I've just defined.

It's for when the potential patient benefit justifies the potential risk of the treatment use so that the risks are not unreasonable in the context of the disease or condition and not unreasonable for the number of patients who are going to be receiving it under expanded access.

Expanded access cannot jeopardize drug development because FDA believes that drug development and drug approval still provide the greatest evidence of risk/benefit and the best access to the most number of patients.

The one question asked, can you have multiple investigational agents under expanded access? There are no prohibitions against use of multiple investigational drugs under expanded access either under one IND or several INDs.

Expanded access to investigational drugs for treatment use are codified under some regulations we call Subpart I, and those regulations have been in effect since 2009 formally, but we've been providing expanded access under these processes really for decades.

Subpart I talks about three categories of expanded access, two of which I think are pertinent for the committee today and tomorrow. That would be individual use, including emergency use, and I'll talk about the differences in the next few slides; use in an intermediate-size populations,

meaning several patients maybe up to a couple of hundred; or a treatment IND or protocol for widespread treatment use, and this is usually when sponsors who are in phase 3 are providing access while their drug is being reviewed before approval.

More evidence of efficacy is needed as the number of people receiving treatment increases. Subpart I also establishes parameters and outlines filing requirements, and I'll talk about a few of those.

Probably the mechanism that is maybe most widely used would be that for individual patients and a licensed physician, any licensed physician may make this request and actually usually becomes the IND holder, the investigator, when a drug sponsor chooses not to hold the IND.

This is usually the case; usually, drug sponsors are not the holder of the IND for individual INDs for single patients. Usually, a physician holds the IND.

The physician determines the probable risk from the drug does not exceed that from the disease

or condition, and FDA determines that the patient cannot obtain the drug under another IND or protocol that's in development.

Non-emergency or emergency use can be granted under these individual patient INDs. For safeguards, treatment is generally limited to one course unless authorized by FDA. If there are a lot of single cases of these single INDs, sometimes a division or FDA will ask a sponsor to put them in an intermediate size protocol or IND.

What is an intermediate size population IND? Usually, the drug sponsor is the IND holder, although a university or a physician could be an intermediate size IND sponsor.

Intermediate size INDs may be needed when a drug is not being developed, the disease is rare, there's really no market for it; it's being developed but patients are not eligible for ongoing clinical trials; or when there is an approved drug but that drug is not available either because it was withdrawn or there are drug shortages.

The criteria is that there should be

sufficient evidence that the drug is safe at the proposed dose and duration to justify the size of the exposed population. There should be some preliminary evidence of efficacy.

There should be an explanation of why the drug cannot be developed or why patients can be enrolled in a clinical trial. Usually, these INDs are reviewed annually to determine whether another mechanism such as a treatment IND might be more appropriate if the drug is under development.

Single-patient INDs, some nuts and bolts. Your physician who needs an investigational drug for a patient with a serious condition, what does that physician do? First of all, they need to identify a sponsor or manufacturer of the drug and ask that sponsor or manufacturer if they will provide the drug and ship the drug to them.

This is part and parcel with permission from the sponsor to allow FDA to refer to any of its files previously submitted to the FDA so FDA can verify that the drug being shipped is the drug that we have looked at before.

Then the investigator would contact the FDA, phone, fax or email -- and I have reference slides for those -- to request an IND. For emergency INDs, FDA is available by phone 24/7. For non-emergency INDs, usually, this is accomplished during business hours.

When an IND is allowed to proceed from FDA and the company has agreed to ship, for emergency use, the paperwork is usually done later and the IND number is use given later during business hours. If it's requested over the weekend, the company ships drug on verbal agreement from FDA.

For single-patient INDs, non-emergency, usually the paperwork is filled out; the IND number is obtained, provided to the sponsor. FDA technically has 30 days to review these, but often these are granted on the same day, usually no more than several days.

During normal business hours, here are the contacts. If a physician doesn't know what division is regulating a certain drug, they can call a general number and find that out, and they

will hook you up with a division who reviews that drug. There's also after-hours contact 24/7, a telephone, and you'll be connected with a physician from a division on-call.

The paperwork, the review divisions can help with this. And I want to make note that earlier this year, there was draft guidance issued on a simplified form called number 3926. Soon physicians will be able to use this one-page, user-friendly form for an initial individual patient expanded access submission.

Right now, until that guidance is finalized, we're still using the old form. Even using the old form, this can be accomplished in an hour or two or less. And if there are any questions, the division is happy to help answer those.

The paperwork is basically Form 1571. It has information regarding the requestor's name and address; the product and the source of the product; a short paragraph on the patient's disease course and why they need the drug, no names or identifiers; the plan treatment course, dose and

duration and plan monitoring; and technical and preclinical information about the product, as I mentioned before, would be supplied by the sponsor or manufacturer via a letter of authorization.

Then there's Form 1572, which is basically just the credentials of the physician who will be administering the drug, so a CV can be attached for that.

What are the sponsor/investigator responsibilities? For emergency use, a sponsor/investigator needs to inform the investigational review board, the IRB, within five working days. For non-emergency conditions, prior IRB approval is needed.

Of course, they will need to obtain informed consent from the patient or family. During the treatment course, the investigator should submit any unexpected serious adverse reactions that are considered related to the drug to the FDA.

At the conclusion of treatment, they are to provide FDA with a written summary of the results of the expanded access; we're talking very simple

summary, you know, patient survived, did well, died, including any adverse effects, talking generally a paragraph, and if dosing for more than a year, submit an annual report to the FDA.

So after the treatment course is over, the investigator can withdraw the IND, and they're free from any additional reporting procedures.

Some summary points, explanation of the processes and parameters for expanded access are clearly outlined under CFR 312, Subpart I, and they're further explained in very user-friendly terms on an FDA website on expanded access compassionate use, and there's the link.

There was a draft guidance that will further simplify these procedures for single-investigator INDs with a new abbreviated form that, hopefully, will be out for use very soon.

There are FDA contacts available 24/7 to assist physicians in submitting single and emergency INDs. The regulatory responsibilities that we have in place we feel are fairly minimal and are really there to protect the safety of the

patient.

With that, I'll end my presentation, and I believe there's time for questions.

Clarifying Questions from the Committee

DR. VENITZ: Thank you, Dr. Murray. We have a little time for questions. Dr. DiGiovanna?

DR. DiGIOVANNA: John DiGiovanna. Thanks for the clarification. I have really two questions about why a sponsor would -- what benefit is it for the sponsor to agree to do this?

If they're in drug development, it would appear that the liability would be uncovering problems that might be related to the drug or might not be related to the drug that would be suggested in an environment that was outside of their control, and in that case, potentially might be a liability for them.

If it was a drug that wasn't being developed because, as you suggested for a rare disease, it may not be economically feasible to do that, why would they do this?

So the first impediment really is to the

physician going to the company -- try to explain to me how this practically works, and do they actually do this very often? Because I deal a lot with rare diseases. and there are sometimes drugs that begin to get approved and then don't get approved, and the patients are clamoring for the drug. And it's unclear from the physician's perspective whether there's anything they can do at all.

DR. MURRAY: Well, companies do do this, and I don't know all of the reasons. Yes, there could be some liability, but I think, to a certain extent, they feel obligated to provide drug for a patient who is in serious need, so they listen to the physician's story of the need.

A lot of times, companies do grant use and shipment of their drug. Now, not all companies do this. It depends on maybe what stage of development they're in. But we've had single-patient INDs for a drug that's really not under development for as long as I've been at the agency and way beyond that, so over 23 years, and it continues. You'd be surprised, but there's a lot

of companies willing to do this.

DR. VENITZ: Thank you. Dr. Vaida and then Dr. Wall.

DR. VAIDA: Yes, I have a question on the sponsor thing too, is that since we're looking at the 503A and 503B, a sponsor has to be the manufacturer? I mean, who else could serve as a sponsor? It looks like the physician could hold the IND.

DR. MURRAY: Right.

DR. VAIDA: But could a 503A or 503B actually be a sponsor?

DR. MURRAY: Right. Yes. So really, anybody could be a sponsor. A sponsor must have investigators so a licensed physician to administer the drug. But it could be a university; it could be a physician; it could be a manufacturer, any of those entities.

DR. VENITZ: Dr. Wall?

DR. WALL: This is to tack on Dr. DiGiovanna's question. Several states, including my own, have passed recent legislation

they'll call last-ditch legislation, which basically says that a manufacturer may sell these substances that are being investigated if a physician approves to the patient for the patient to use, which makes it sound like it's out of any of the IND process at all.

Is that correct? Have you guys had experience with that, or can you comment on what we're seeing in multiple states?

DR. MURRAY: All that I've been seeing, and others may want to comment, is that when investigational drugs are given to patients, they're done under the IND process, and so they're administered under IND. So we get the request and we go through the process as described.

Any other comments?

MS. AXELRAD: We can't really comment on what various states may be doing here, but as Dr. Murray indicated, our position is that it's either compounded in accordance with the conditions of 503A, meaning you couldn't do something that's on the list of drugs that have been withdrawn or

removed from the market for safety reasons or it's with something that meet the conditions with regard to the bulk drug substance, or it has to be under an IND. And that's what federal law says.

So regardless of what state laws might be saying you can do, we would view federal law as -- we would enforce the federal law.

DR. VENITZ: Dr. Davidson?

MS. DAVIDSON: So under the context of our discussion here, this issue arose when we were discussing drugs placed on the Do Not Compound list, which implies they're no long commercially available; there is not a sponsor. Even if there is a sponsor, they don't have it anymore. So I think Allen answered my first question that a 503A or B person could serve as a sponsor.

But my other question is, first of all, do the drugs on the Do Not Compound list, are they eligible for a specific patient need? I believe it was chloramphenicol that raised this issue in our original discussions. Then my second question is, could this potentially also apply to candidates

that were denied addition to the positive list of bulk substances that can be compounded with if a patient need arose?

MS. AXELRAD: Dr. Davidson, let me address that. Yes, it can apply to any drug, assuming that someone can get the drug or the substance to do it. If you submit an IND, you can do it. And as we indicated, as Dr. Murray indicated, anybody can be the holder; it could be an individual physician; it could be an academic institution; it could be a manufacturer; it could be a compounder.

Basically, that's why we're spending time, I think, on this subject here, is that there was concern expressed at the last meeting about whether if something was put on the withdrawn or removed list or not put on the bulk drug substance list, whether that was fair to patients who might be taking the drug.

Our answer is that we have a mechanism for that, and that is an IND. I think, as Dr. Murray said, it's really important to recognize that the IND mechanism was set up to protect patients so

that people are not experimenting on patients, so that there's some understanding of the quality of the drug before they get it, the chemistry and toxicology of the drug, so that an informed decision can be made about whether the benefits of the drug outweigh the risks, which can be quite substantial if you don't know much about the drug because it hasn't gone through a long development process; it hasn't gone through the approval process.

The other, part of it is, it's informed consent. If a patient is going to be given a drug for which the agency has made a determination that it's unsafe and that manufacturers can no longer provide that drug to patients, they need to be informed of the risks of the drug before they get it. Somebody has to make an informed decision about whether it's likely that the benefits of the drug would outweigh the risks.

That's why we think it's important that we understand that there is a mechanism available, why it's made available under those circumstances, and

how it would work.

DR. VENITZ: Dr. Carome?

DR. CAROME: Mike Carome. If I understand correctly, a single-patient IND could be the first IND for a product or would it have to already be an entity that held an IND for that drug?

DR. MURRAY: Occasionally, they are the first IND. If that's the case, usually, we would have pre-IND information or maybe some drug master file from a sponsor, so another submission. It's not the usual case where it's the first IND, but it has been in the past.

DR. VENITZ: Dr. DiGiovanna?

DR. DiGIOVANNA: John DiGiovanna. To clarify the broad picture for me from what we have done in the last meeting, one of the drugs that we voted to not have on the Do Not Compound list was cantharidin, which have been available for a very long period of time. But I don't believe it's on the bulk substances list, although it's been around for many, many, many years.

Does that mean that it can be compounded now

by an individual pharmacy by prescription or does it mean it would need to be used via this IND mechanism?

MS. AXELRAD: Well, let's talk about the situation. I'm going to talk about the process and some other issues associated with the bulks list later. But let's just say that we are down the road and we put cantharidin on the list. We have to go through a proposed rule and get comments, and then put out a final rule.

Let's say we put out a final rule that says cantharidin is on the list. Then it can be compounded without an IND. It's exempt from the new drug approval requirements under Section 503A. It could be compounded by a compounder under Section 503A once it is on the bulk drug substance list. And then this afternoon, we'll talk a little about our process and what's happening in the meantime before we make final decisions on the drugs.

DR. VENITZ: Mr. Mixon?

MR. MIXON: Thank you, Dr. Venitz. Can we

talk specifically about domperidone and walk through the steps that a physician would have to go through?

MS. AXELRAD: No. Dr. Murray I don't think is in a position to talk about that specific drug.

MR. MIXON: Can we pick another hypothetical drug?

MS. AXELRAD: A hypothetical drug, not that specific one?

MR. MIXON: Well, in my world, this drug comes up all the time and compounders are asked to compound it all the time. And as you well know, many compounders are compounding it. The legal mechanism, as I understand it, to obtain this drug is to go through the IND process.

My interest is in helping to educate other pharmacists to the correct way to obtain this drug. I'm just curious, one, is there a sponsor? If a physician calls, is there a sponsor?

MS. AXELRAD: Okay. I can address that because we've had a lot of inquiries. Domperidone is a drug that was never approved in the

United States for anything. It has been studied -- correct me if I'm -- I'll keep going, and she can correct -- okay, back me up.

Anyway, it is available under an expanded access IND, but it is a manufactured product that's manufactured by two companies. One is in the UK, and I think the other one is in Canada.

Also, there is a pharmacy, Dougherty's Pharmacy, that does not compound it, but it gets the manufactured product from the manufacturers and then makes it available. It's available for very specific GI uses.

But what we've seen is that compounding pharmacies have been offering this for lactation. And we issued a safety warning in I think it was 2004, because we were concerned about the safety impacts of using it for that particular use.

We have basically said that it can't be compounded and we're taking action. We've cited a number of compounding pharmacies for compounding with domperidone because of the safety concerns we

have associated with that product.

It is available for appropriate uses, for GI use under an expanded access protocol, but it is the manufactured drug that is made available for those uses, not a compounded product.

DR. KORVICK: Excuse me. I don't --

MR. MIXON: Well, my interest --

DR. KORVICK: Can I add one more thing? I'm Dr. Korvick. I'm the deputy director of the Division of Gastroenterology and Inborn Errors Products. And one additional aspect to what Jane was talking about is that because of some of these safety issues, there's an import alert as well.

If these are coming into the country in other ways outside of the IND process, you may be subject to those drugs not making it to the patients. So there is also an import alert for some of the safety reasons that Jane has mentioned. Thank you.

DR. VENITZ: Thank you.

MR. MIXON: My interest is only in use for gastroparesis or GERD. But if I have an

gastroenterologist in my community and I say to him, you can't ask me to compound it and I won't compound it, but you can go through the IND process, their typical response is, "I don't have time for all that paperwork." That's why I'm bringing this up. You know, the other alternative is that we refer these people to the Canadian drug market.

MS. AXELRAD: They don't have to go through any paperwork. They can get it from -- I believe it's Dougherty's Pharmacy in Texas.

DR. KORVICK: They do have to go through the IND paperwork, but our division has worked very hard to streamline and expedite what the paperwork needs to be, and we work with the physician. I don't know how we can make physicians understand, but we are there to help them with some paperwork if any paperwork is an impediment then. But we've tried to streamline the whole process, so it shouldn't be an impediment to the practicing physician.

MR. MIXON: Well, obviously, I don't have

any firsthand experience with trying to file the paperwork, but this is the excuse normally.

So the entry point for the local gastroenterologist would be the phone number that's provided on the slide earlier?

DR. KORVICK: It's on the FDA website. You can find it. We can get you that information.

MS. AXELRAD: We can provide the link to that. There's a link that shows -- that specifically talks about the expanded access protocol for domperidone and how you can get it.

DR. VENITZ: Dr. Jungman?

MS. JUNGMAN: Dr. Murray, something that didn't appear in your slides, what was discussed in the background materials a little bit, is the IRB process. And I was hoping you could maybe talk a little about any requirement for IRB review and how that might affect patient access.

DR. MURRAY: Well, for single-patient INDs, it's non-emergency use, so IRB approval is needed. Like I said, for emergency use, the IRB can be informed within five working days. If it's

life-threatening, meaning that if the patient doesn't get treated, they will die or experience serious morbidity in the next couple of weeks, then you can have an emergency IND, just inform the IRB.

So it would be the usual IRB review process. A lot of IRBs do have kind of expedited review or different procedures for single-patient INDs. They have their regular meeting schedule for the larger protocols, but it would be just according to the local IRB. And that's kind of a local requirement.

MS. JUNGMAN: But what happens in situations where an IRB is not readily accessible, so something -- the FDA's Q&A document recognizes that there are circumstances where an investigator might not be looped in with their local IRB.

DR. MURRAY: Well, sometimes our central IRBs or sometimes the drug sponsor might have a central IRB set up. There are other mechanisms on a case-by-case basis. I think the division can help provide some information about that, but it is still the local responsibility of the IRB. The local IRB has -- it's their domain first before a

central IRB if there's a local IRB available.

MS. JUNGMAN: I guess what I'm trying to get a sense of, though, is whether this is a realistic -- the process is a realistic prospect for a physician that's, say, is out in the community and you're talking about a compounded drug where there's not a sponsor. How would the IRB requirement play out in that kind of circumstance?

DR. MURRAY: Well, I believe it's realistic because we have a lot of single- and emergency-patient INDs that go through our division probably to the tune of a hundred to maybe several hundred per year.

MS. JUNGMAN: For compounded products though?

DR. MURRAY: So it seems that the IRB review gets in. And I said for emergency IND, it's certainly easier.

MS. JUNGMAN: Okay. Thank you.

DR. VENITZ: Dr. Pham?

DR. PHAM: Just going back to the

availability implications, because on the hospital side, especially in pediatrics, we'll probably often see the rare disease state, if that's an oxymoron, regarding like orphan drugs. We've definitely used IND. We've been impressed actually with the turnaround for that specific use.

Drug shortages also have played a part in where that could come into play, but I think when it comes down to -- Robert DeChristoforo, I think, commented previously -- specifically with chloramphenicol question the last time and the capsules not being available. But still there was -- I think he had commented at the NIH they had compounded a couple of times within a year.

So clearly, there is still probably, I assume, the base powder available, as is the case with a lot of the compounded products. There are some sort of chemical entity to the USP grade of bulk powder, and that's what's used.

So I guess with the IND and availability, if something goes on the Do Not Compound list and that company that made that bulk powder sees that, would

that then take that out of the market, and what would be the delay if, say, that product capsule had to be acquired from the UK?

I assume for drug shortages, that process has kind of been expedited, but I don't know if it makes a difference if it's a compounded -- I guess a raw ingredient for a compound compared to, say, if I got calcium chloride from France for a drug shortage.

MS. AXELRAD: I'm not sure how to address your question. I think that the availability of bulk compounds for compounding is sort of separate from whatever you do with this. Either the sponsor is going to keep making the drug or they're not. Either they're going to sell it to somebody who wants to do something with it other than whatever they're doing or they're not.

I think it's sort of independent of whether you decide whether something goes on the list or not. If a sponsor's drug has been withdrawn or removed from the market for safety reasons, unless they're conducting a study for it under an

investigational drug application for something else, it probably won't be available from the sponsor.

In some cases, the sponsor may choose not to make it available anyway, so anybody who wants to use it, whether for a compounding or under an IND would have to get it from somewhere else.

DR. VENITZ: Okay. One more question. Dr. Braunstein?

DR. BRAUNSTEIN: I just wanted to point out that some of these compounds, these chemicals, are available for other nonhuman use. It's up to, obviously, the manufacturer as to whether or not they would make those available. But not all of these compounds or chemicals are only for human use, and I think that's -- that's certainly the distinction. The FDA would not be regulating nonhuman use of the product.

DR. VENITZ: Okay. Thank you, Dr. Murray. We appreciate it.

We are now going to go switch topics and proceed with the FDA presentation on the withdrawn

or removed list process from Gail Bormel. She's the acting director of the Division of Prescription Drugs within the Office of Unapproved Drugs and Labeling Compliance.

Presentation - Gail Bormel

MS. BORMEL: Good morning. I'm Gail Bormel. As Dr. Venitz said, I'm the acting director of the Division of Prescription Drugs in the Office of Unapproved Drugs and Labeling Compliance in CDER's Office of Compliance.

Today, what I'm going to talk about is the process to identify candidates for or amendments to the withdrawn or removed list. First though, I'm going to provide a little bit of background on the withdrawn or removed list.

Both Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act require the agency to publish a list of drugs that have been withdrawn or removed from the market because the drugs or components of the drugs had been found to be unsafe or not effective. We call that the withdrawn or removed list.

The statute explains that the drugs that appear on this list should not be compounded. If they are compounded, the compounded drug cannot qualify for certain exemptions from statutory requirements that are described in Sections 503A and 503B.

We went through this pretty extensively at the last meeting in February, and if you would like to review that, there's additional background on our website, and the address is on this slide.

But just to go over a little bit more information about the individual sections of the Act that deal with compounding, Section 503A describes the conditions under which compounded human drug products that are made by state-licensed pharmacies are entitled to exemptions from three statutory requirements.

They are: the FDA approval prior to marketing, which is in Section 505 of the Act; compliance with current good manufacturing practice requirements in Section 501(a)(2)(B); and labeling with adequate directions for use in

Section 502(f)(1). So if a compounded drug is made under the conditions described in Section 503A, they'd be exempt; they would qualify for exemptions from these three sections.

It's important to note that pharmacies that qualify for the exemptions are primarily regulated by the states, but there are federal requirements that still apply. For example, drugs cannot be made under unsanitary conditions, and that requirement is in Section 501(a)(2)(A) of the Act.

Now, we'll turn to Section 503B. Section 503B of the Federal Food, Drug, and Cosmetic Act was added by the Drug Quality and Security Act that was signed into law in November 2013. This section creates a new category of compounders known as outsourcing facilities. Registered outsourcing facilities have to comply with CGMP requirements and are inspected by the agency according to a risk based schedule.

In addition, drugs that are compounded by outsourcing facilities in accordance with the conditions described in Section 503B can qualify

for exemptions from these statutory requirements: the new drug approval requirements under Section 505; the requirement that the product labeling bear adequate directions for use under a 502(f)(1); and the drug supply chain security requirements in Section 582 of the Food, Drug, and Cosmetic Act.

As I mentioned earlier, what I'm going to talk about is the process to identify drugs for the withdrawn or removed list. This would include new candidates and possible amendments to the drugs on the withdrawn or removed list.

To identify these candidates, FDA periodically reviews available information on drugs that have been withdrawn or removed from the market because they have been found to be unsafe or not effective.

This slide and the next one shows the types of information that the agency reviews. As you can see from this slide, we look at Federal Register notices announcing withdrawal of approval of a drug application for safety or effectiveness reasons. We also take a look at notices announcing an agency

determination that a drug product was removed from sale for reasons of safety or effectiveness.

Other information that the agency reviews may include FDA alerts, drug safety communications, news releases, public health advisories, healthcare practitioner letters, citizen petitions, and sponsor letters.

FDA also reviews available information to determine whether any new drug applications have been approved for a drug product containing, as an active ingredient, any of the drugs on the list to determine whether any of the drug entities on this list should be modified to account for the new safety and effective determination and approval.

For example, a drug may have been approved in a new formulation, indication, route of administration, or dosage form since the list was last revised. And if that's done, FDA can consider proposing a modification to the list to remove the drug from the list or to exclude the particular formulation, indication, route of administration, or dosage form.

We saw that at the last meeting. Bromfenac was on the list, already on the withdrawn or removed list, and at the last February 2015 meeting, we excluded the ophthalmic solution from the withdrawn or removed list. So that was a modification that was made or proposed for the withdrawn or removed list.

Well, what happens once the agency has identified drugs for the withdrawn or removed list? Well, what is done next is that appropriate divisions within the Office of New Drugs will evaluate each identified candidate or modification using the information that we found or that is available for the drug.

The responsible division will prepare a review of the information that documents its recommendations as to whether to include the drug on the withdrawn or removed list, or to remove a drug from the list, or to modify an entry.

This slide really describes the previous process that the agency used to update the withdrawn or removed list. In the past, FDA has

published a notice of proposed rulemaking to add identified drug products to the list or to modify existing entries before consulting the advisory committee.

As you can see, in October 1998, FDA used rulemaking to develop the original list and consulted the committee about the list before finalizing the rule. In July 2014, the agency issued a proposed rulemaking identifying 25 drugs to add to the list and one drug entry to modify on the original list.

FDA then consulted the committee on the drugs identified in the July proposed rulemaking back in February 2015. In addition, what the agency said in the July 2014 Federal Register notice was that we were inviting comments on an alternative procedure to rulemaking to update the list in the future.

As we said in the July 2014 notice, the agency is considering its process to update the withdrawn or removed list going forward, and we will announce that process in the final rule.

That concludes my presentation on the process to identify candidates for the withdrawn or removed list, and we're going to turn to what we're actually going to look at, at this meeting.

We have identified four new drug candidates for the advisory committee to review, which may eventually be included in an update to the withdrawn or removed list.

At this meeting, we're going to consider inclusion on the list of the following four drugs: acetaminophen, all drugs products containing more than 325 milligrams of acetaminophen per dosage unit;

Aprotinin, all drug products containing aprotinin;

Number 3 is ondansetron hydrochloride, all IV drug products containing greater than a 16-milligram single-dose of ondansetron hydrochloride;

And the last is bromocriptine mesylate, all drug products containing bromocriptine mesylate for prevention of physiological lactation.

I'm available if you have any questions

before we turn to the presentations.

Clarifying Questions from the Committee

DR. VENITZ: Yes, we have a few minutes. Are there any questions? Yes?

DR. VAIDA: Allen Vaida. On slide 8 that you had with the -- it could be either the route of administration, or dosage form or indication. You had mentioned at the last meeting, we had excluded like an ophthalmic use --

MS. BORMEL: Right.

DR. VAIDA: -- which is pretty straightforward if you received a prescription for that. But for the indication, if drugs are going to be considered for indication, does the FDA -- would that mean that the physician would have to write an indication for what the drug would be used for?

Because if the drug could still be compounded like -- or the pharmacy would have to tell the patient also -- like is that in your authority that that would have to go along, because how would the compounder know?

MS. BORMEL: Well, I think that what is contemplated under Section 503A is that there is the patient-physician-pharmacy relationship. If a pharmacist is compounding drug products that are on the withdrawn or removed list for a particular -- that are on the withdrawn or removed list because there's a particular indication that cannot be compounded, the pharmacist would need to find out about what that product is being compounded for.

DR. VAIDA: Okay. So you're just taking -- there's nothing that's going to be regulated with that. It's just hoping that that'll happen? I'm just saying -- I mean, there's not indications now on a lot of prescriptions and, I'm just curious.

MS. BORMEL: Right. There are not routinely indications. I mean, it's not in the law, but there is a professional responsibility for pharmacists when they compound. If there's something that's put on the list that the product should not be compounded, then it's something that

the pharmacist needs to be aware of and to investigate further.

MS. AXELRAD: If I can take a shot at this, I think that it's likely that -- we will try and write the list in a clear way. For example, most of the drugs are simply there as the drug, without any qualification. Some of them, the criteria are obvious, like we're going to talk about acetaminophen with more than 325 milligrams in any single dosage unit; that's obvious. If it's for an ophthalmic use, if it's allowed for an ophthalmic use but others are not, that's obvious, route of administration.

I think to the extent that if we get into something where we think it's unsafe, it's been found to be unsafe for a particular indication but it's allowed for other indications, I think that we would just have to write it clearly enough.

If it says don't use it for this indication but you can use it for something else, I think that we would expect the pharmacist to get something from the doctor that indicates that it's going to

be used for -- not going to be used for the indication for which it's listed.

So I think that we have to write it clearly, and then they have to make sure that that it isn't going to be used for something that's unsafe. I mean again, I think -- as Gail said, it really -- the pharmacist has a responsibility for that, and the doctor. And we would expect that if it's unclear, and the pharmacist has a list of drugs that have been withdrawn or removed for safety reasons, and it says, don't use for this indication, that if they get a prescription, they would have a conversation about that with the physician or the prescriber.

DR. VENITZ: Dr. Braunstein?

DR. BRAUNSTEIN: But doesn't that fall under labeling? Because 503As are -- they are exempted from the labeling requirements. When we manufacture a drug, for example, and it's a new drug and we work out labeling with the FDA, there might be a statement, "Not to be used for X," right? And that's something that we would

understand. It doesn't say that a physician -- then it's fair warning for the physician.

I'm not so sure -- I'm not a lawyer so I'm not -- but I'm just concerned that we're treading on a line here that gets into that exemption, and I don't know how that will all be resolved.

MS. BORMEL: Well, I think that drugs that are compounded in accordance with Section 503A qualify for the exemptions of the Act including 502(f)(1), which is adequate directions for use. But if we're putting something on a Do Not Compound list for a certain indication, we're saying that that should not be compounded. That would be a condition. In my mind, it will be a condition of Section 503A.

DR. VENITZ: Dr. Jungman?

MS. JUNGMAN: I'm just wondering how this would play out differently for 503Bs where you might be producing standard stocks of drugs, and so there wouldn't be that expectation of relationship between the physician and the pharmacist.

MS. AXELRAD: We're not talking about 503B -- well, I guess the withdrawn or removed list does deal with both.

MS. BORMEL: Yes. But 503B is a little bit -- we haven't gotten to that yet, but the bulk drug substances that can be used under Section 503B are either drugs for which there's a clinical need or drugs that are in shortage. It's a little bit different. When we get to that section, we can talk a little bit more about that. I don't know that we're going to be addressing at this particular meeting.

MS. AXELRAD: Well, since the list that we're doing does apply to both 503A and 503B, it's relevant. But as Gail said, in order to compound from a bulk, a 503B outsourcing facility, it has to be on a list. So it either has to be on the drug shortage list, for which case they can do it, or it has to be on a list that we've determined there is a clinical need to compound from using the bulk. I think when we look at the bulks that they can use, we'll have to deal with that.

In terms of compounding from an approved product, for example, I think that that's something that we'll just sort of have to figure out, how that's going to work.

I think that it would be best if we have this discussion when we talk about bromocriptine maleate [sic], which is the drug that we're going to be talking about that's been found to be unsafe for a particular indication but is available for other indications.

I think that we can have some discussion and we'll be interested in hearing your views about what you think we ought to do about that. You can decide and recommend that we not put it on the list of withdrawn or removed products because you think it should be used however which way they want or because it might be difficult for somebody like a 503B to determine what indication it's going to be used for.

But I think those are things that we can take up. I think it's good to work through these things with a specific example, and we actually do

have one today.

DR. VENITZ: Thank you. Any further question for Ms. Bormel?

(No response.)

DR. VENITZ: Okay, then thank you again. As she already indicated, we're now going to move into our specific compounds. The first one is acetaminophen, and Dr. Sharon Hertz, director of the Division of Anesthesia, Analgesia, and Addiction products, will present on the recommendation.

Presentation - Sharon Hertz

DR. HERTZ: Thank you. Good morning. I'm going to be speaking about acetaminophen. It's, of course, one of the most commonly used drugs in the U.S. for treating pain and fever. The hydrocodone-acetaminophen combination products have been the most frequently prescribed drug for nearly 20 years in this country.

Exceeding the maximum daily dose of 4 grams of acetaminophen places patients at risk for serious liver injury that can lead to liver failure

and death, and acetaminophen-related hepatotoxicity has been a leading cause of acute liver failure in the U.S. And that's why we're here to discuss this today.

There are a number of factors that lead to acetaminophen-related liver failure. One is the large number and variety of over-the-counter and prescription acetaminophen products and indications. Consumers have unintentionally overdosed by taking more than one product that contains acetaminophen at the same time without realizing they were duplicating the acetaminophen.

Patients were often unaware that their prescription products contained acetaminophen as the pharmacy drug containers often only use the letters, APAP, an acronym for the chemical name or an abbreviation such as ACET.

Patients may take more than the maximum number of labeled or prescribed doses seeking greater therapeutic benefit, also unaware that they're placing themselves at risk.

Another important factor is that the

symptoms of liver damage can take days to emerge and are not readily recognized as the result of acetaminophen poisoning generally by patients or clinicians early on; they can mimic flu symptoms.

The antidote for acetaminophen overdose can be very effective, N-acetylcysteine, but it has to be given soon after the overdose, preferably within the first 8 hours; need benefit up to 24. But after that, it's unclear that the problem can be reversed.

We don't have an exact amount of acetaminophen that causes irreversible liver injury in all circumstances. That specific threshold has not been established and, in fact, may not be the same for all persons in all situations. But that's because, in part, all of the factors that may be responsible have not yet been identified, particularly factors that may result in toxicity near the current recommended total daily dose of 4 grams.

FDA has been active over a number of years trying to reduce the risk of acetaminophen-related

liver injury. There was an advisory committee back in 2002 that agreed there should be labeling changes.

In 2004, FDA engaged in a public education campaign. We asked the state boards of pharmacy to require use of the full word "acetaminophen" instead of shorter terms on the pharmacy containers and to instruct patients on safe use, the important principles of not using multiple products with acetaminophen, not to exceed the maximum daily dose to avoid concurrent alcohol use.

In 2006, we proposed regulations for over-the-counter labeling to include safety information on the container and out-of-carton to also clearly identify the presence of acetaminophen. That was followed by a working group that was established, which led to another advisory committee in 2009.

I'm going to go over this slowly because this was a very important set of ideas that we considered when making our final recommendation on what to do with prescription products.

At the 2009 advisory committee, data were presented, first, that in combination, with an opioid in particular, there really was no evidence to support that the 325-milligram dose -- this has been reversed -- but that the 500-milligram dose provides greater efficacy in a substantial way than the 325. Basically, we did not have data that shows an important dose response when in combination with an opioid.

What I'll explain next is why we thought that there was a substantial opportunity to reduce risk by reducing the amount of acetaminophen per dosage unit from 500 milligrams to 325. Back in 2009 when we looked into this, most of the prescribing of acetaminophen-containing prescription products were 500-milligram-containing products.

If you look at the data on intentional overdose, approximately 72 percent took up to 25 pills. At 500 milligrams per pill, that's a 12 and a half gram dose. That would translate to 8.1 grams at the lower-strength pill. That's a

potential opportunity to save some individuals from injury, although 8 is still a very high dose.

With the unintentional overdose situation, we found that 39 percent of patients knew that they were taking more than recommended, but generally felt they needed more medication for the therapeutic effect. And in this setting, the mean dose associated with hepatotoxicity was 6.5 grams per day.

Changing this from 500 to 325 milligrams per dosage unit brought that down to what would have been an average or mean of 4.2 grams per day. This was really where we thought we could have a big impact with this type of change.

Reviewing the data and the advisory committee discussion, FDA, we concluded that acetaminophen-containing prescription products with more than 325 milligrams of acetaminophen per dosage unit do not provide sufficient margin of safety to protect the public against the serious risk of acetaminophen-induced liver injury. That was published in the Federal Register.

We then went through a process to ask sponsors to limit the dose to 325 per dosage unit. There was a process provided to submit the request withdrawing approval for applications with more than that amount of acetaminophen. This process was completed in July of 2014.

For today, our recommendation is because approvals of applications for prescription drug products containing more than 325 milligrams of acetaminophen per dosage unit have been withdrawn by FDA for safety reasons, FDA recommends the following entry for acetaminophen to be added to the withdrawn or removed list. Thank you.

Clarifying Questions from the Committee

DR. VENITZ: Thank you, Dr. Hertz. We have a few minutes for clarifying questions. This is just to ask any clarifications about the presentation because we'll have discussion of all products when we get through all the presentations.

Yes, Dr. Wall?

DR. WALL: Just a point of clarification, this keeps referring to dosage units. Are you

referring to only oral dosage units? Because as we know, we can have, now -- 1 gram IV piggybacks come premade, which I think of as in dosage unit. We have suppositories. Can we clarify that this is only oral dosage units that we're referring to?

DR. HERTZ: No, it's not. It's also for suppositories -- well, it's for prescription products. I don't believe there are prescription suppositories. The over-the-counter process is a separate one. This is for prescription products.

I am aware of the parenterals. That's a different setting. We hope that in a setting of parenteral use, where it's directly administered through healthcare providers -- nursing staff, physicians -- that there is an adequate accounting of acetaminophen in all forms in that setting. So we think that a dose of a gram can be provided safely in that setting.

DR. WALL: Thank you. I just think we need a little clarification just so that the people know going forward.

DR. HERTZ: Sure.

DR. VENITZ: Dr. Vaida?

DR. VAIDA: No, that's fine. I just wanted a clarification on this is prescription, not over-the-counter.

DR. HERTZ: Yes. This is prescription.

DR. VENITZ: Any other clarifying questions?

(No response.)

Okay. Thank you again, Dr. Hertz.

So the next presentation is on aprotinin, and we have Dr. Kathy Robie Suh. She's the lead medical officer, the Division of Hematology Products to present.

Presentation - Kathy Robie Suh

DR. ROBIE SUH: Good morning. My name is Kathy Robie Suh. I am a clinical team leader in the Division of Hematology Products in CDER. Today, I will present the assessment for aprotinin.

This slide shows an outline of my presentation. First, I will briefly describe aprotinin and its labeled use and a summary of its safety profile. Next, I will give a brief regulatory history with information contributing to

the determination. And finally, I will summarize the rationale for the FDA determination that aprotinin was withdrawn from the market due to safety concerns.

Aprotinin is a polypeptide proteinase inhibitor derived from beef lung. It has a molecular weight of about 6500 daltons. It acts by modulating the systemic inflammatory response in fibrinolysis in thrombin generation. It is administered intravenously and is metabolized with a half-life of about 150 minutes.

Aprotinin was approved in 1993 for prophylactic use to reduce perioperative blood loss in the need for blood transfusion in patients undergoing cardiopulmonary bypass in the course of coronary artery bypass graft surgery, that's CABG surgery, who are at increased risk for blood loss and blood transfusion. That was its only indication.

Major adverse reactions that had been found to be associated with aprotinin in clinical studies and postmarketing experience are shown in this

slide. The first two listed items, hypersensitivity reactions and renal dysfunction, come from the premarketing studies and are included in the aprotinin label. The third listed risk for death with a frequency greater than other antifibrinolytics used during CABG with CPB emerged during the postmarketing period.

In the next several slides, I will present the regulatory history of this new safety information.

This slide lists the most important events and the relevant regulatory history leading to withdrawal of aprotinin from the market. The next several slides give highlights of each of these events beginning in January 2006 and leading to withdrawal of aprotinin from marketing in November 2007.

In January 2006, a publication in the New England Journal of Medicine reported more adverse reactions with the use of aprotinin compared to other anti-fibrinolytic therapy or no anti-fibrinolytic therapy in CABG with CPB in an

observational study.

This study was a retrospective analysis of risk associated with anti-fibrinolytic therapy with cardiac surgery and compared risks for aprotinin with the risks for aminocaproic acid, tranexamic acid, or no anti-fibrinolytic therapy.

The study found a statistically greater likelihood of the development of renal dysfunction and the need for hemodialysis, stroke, encephalopathy, myocardial infarction, and congestive heart failure in patients treated with aprotinin than in those treated with the other anti-fibrinolytic drugs or no anti-fibrinolytic drugs.

As a result of this new information, aprotinin safety was discussed at a meeting of the Cardiovascular and Renal Products Advisory Committee in September 2006. The committee concluded that the overall benefit/risk for aprotinin remained adequate to support marketing.

Shortly after the advisory committee meeting, the agency was informed that an additional

observational study of risks associated with aprotinin therapy had also been completed. This study was called the i3 study shown here on this slide.

The i3 study was a retrospective analysis of a hospital database, the Premier Perspective Comparative Database commissioned by the manufacturer of aprotinin. The way that it had been completed prior to the September 2006 advisory committee meeting, its existence was not mentioned at that meeting.

For this study, the premier database was evaluated for the outcomes of patients undergoing coronary artery bypass graft surgery treated with aprotinin or other anti-fibrinolytics. The study concluded that there was an increased risk of in-hospital death in the aprotinin-treated patients as compared to in patients treated with aminocaproic acid.

In September 2007, a joint meeting of the Cardiovascular and Renal Products and the Drug Safety and Risk Management Advisory Committees was

convened to discuss the updated safety information for aprotinin.

Discussions centered around the newly announced i3 study report and emerging information from an ongoing prospective clinical trial of aprotinin in cardiac surgery termed, BART study. The committee concluded that the additional information at that time was not persuasive to change the benefit/risk for aprotinin. However, the committee recommended that safety be reevaluated at the completion of the BART study.

This slide briefly summarizes the BART study. It was initiated in August 2002 and was terminated in October 2008. This was a prospective randomized trial of aprotinin, tranexamic acid, and aminocaproic acid in patients undergoing CABG surgery with cardiopulmonary bypass in Canada.

The trial was terminated early upon recommendation of the Data Monitoring and Safety Committee due to a finding of greater frequency of death in patients treated with aprotinin, about 6 percent, compared to those treated in the

combined tranexamic acid plus aminocaproic acid group, 3.9 percent.

Subsequently, in November 2007, the sponsor agreed to remove aprotinin from marketing worldwide. Continued access to aprotinin for use in certain surgical patients with an established medical need was provided by the sponsor via an open-label treatment protocol.

In conclusion, this slide summarizes the safety issues that contributed to the marketing discontinuation of aprotinin.

These reasons include increased in deaths with use of aprotinin compared to those both with aminocaproic acid and tranexamic acid, renal adverse events and deaths due to anaphylaxis, and improvements in safety of blood supply with respect to infection risk.

Based on the total available information, the agency is recommending that aprotinin be included on the list for non-compounding with the recommended entry, aprotinin, all drugs containing aprotinin. This concludes my talk.

Clarifying Questions from the Committee

DR. VENITZ: Thank you, Dr. Suh. Any clarifying questions? Dr. DiGiovanna?

DR. DiGIOVANNA: John DiGiovanna. On your second to last slide, it notes November 2007, that the sponsor arranged for continued access for use with certain surgical patients with an established need. Is there any result of that? Are there any subgroups of patients that have this specific unusual need?

DR. ROBIE SUH: That protocol was opened and was listed, but to my knowledge, results of that have not been published.

DR. VENITZ: Mr. Mixon?

MR. MIXON: Bill Mixon. Are you aware of anyone that's compounding this drug now?

DR. ROBIE SUH: I am not.

MS. AXELRAD: For most of the drugs that we -- like certainly the 25 that we did the last time, we've said in the proposed rule that we're really not aware of people doing this. We don't know of anybody doing it by and large, but there

may be some.

People don't tell us what they're compounding. We don't even know if people are compounding under 503A because they generally don't register with us. And they're not listing their drug, so we don't really know.

MR. MIXON: I'm just curious why it made the list.

MS. AXELRAD: Pardon me?

DR. ROBIE SUH: I would just say it's a very limited use within a very distinct setting as opposed to a general --

MS. AXELRAD: Well, we're putting anything on the list that we identified --

DR. ROBIE SUH: I understand --

MS. AXELRAD: Any drug, regardless of whether it is -- since we don't know what people are using to compound and since the statute says that we should develop a list of drugs that have been withdrawn or removed from the market because they've been found to be unsafe or ineffective, we have been trying to identify any drugs that we know

of that have been withdrawn because they've been found to be unsafe and putting them on the list regardless of whether we know of anybody compounding them or not. That's just sort of the nature of the list.

DR. VENITZ: Dr. DiGiovanna?

DR. DiGIOVANNA: I'm trying to get my head around the whole process a bit, and it seems, at some point, that you're trying to remove any drug that has ever had a toxicity but doesn't have an established efficacy. And I wonder about scenarios like this where -- I don't do coronary pulmonary bypass. It would be interesting to know what those patients had that they seem to have some benefit from this, and then now it's potentially not available.

While it appears that it's not being compounded widely or proposing a risk, it seems that the position is to remove a whole lot of drugs and not be aware of those scenarios where they could be of use.

I'm just trying to get my head around the

thinking about this, whether it's preferred to remove everything or what happens in the scenario where apparently someone did a study thinking that there was some value to it, and we just don't know what the result of it was.

DR. VENITZ: Dr. Suh, do you want to respond?

DR. ROBIE SUH: Are you asking for this particular product? I thought it was a more general question.

MS. AXELRAD: I thought Dr. Gulur might be prepared to address that.

DR. ROBIE SUH: I'm sorry.

MS. AXELRAD: Were you going to?

DR. GULUR: Yes. I'd just like to comment on the use of aprotinin right now, is, I would say, just not being done in coronary bypass grafts. I don't do the surgery myself, but I do provide the anesthetic for it. And I can tell you that it's not used. There are alternatives and those alternatives are usually more than adequate for the patient populations in general.

Is there a pocket somewhere? Is there a single patient? I can't speak to that, but I definitely know that there's no established medical protocol for patients who need aprotinin as opposed to other existing options.

I just like to say, maybe just to add, that I read this to mean something more like if there was a special case, even if there was, we do have that IND expanded access option available, so it would be very similar.

MS. AXELRAD: That was my answer.

DR. VENITZ: Just to add to that, that's the way I read this too. Even if you take it on, put it on the to-be removed list, there is a protocol in place that the manufacturer provides it. So you don't really need to compound it even if it were to serve a sub-population and provide a benefit.

Any other clarifying questions for Dr. Suh?

(No response.)

Thank you very much, Dr. Suh.

Let's move on to our next compound, ondansetron. Dr. Karyn Berry, medical officer with

the Division of Gastroenterology and Inborn Errors Products, she will present on ondansetron.

Presentation - Karyn Berry

DR. BERRY: Good morning. Again, my name is Karyn Berry, and I'm a medical officer in the Division of Gastroenterology and Inborn Error Products. Today, I will provide background information on intravenous ondansetron and the recent regulatory history of the drug product. Then I will discuss the main focus of this presentation, which is the rationale for the FDA's determination that the IV ondansetron 32-milligram dose was withdrawn from the market because it was found to be unsafe.

Although the 32-milligram single-dose was withdrawn, intravenous ondansetron remains approved and is still marketed in the U.S. at lower dosage with no single IV dose to exceed 16 milligrams.

IV ondansetron was initially approved in 1991 as Zofran. It is a selective 5-HT3 receptor antagonist and is extensively metabolized with approximately 5 percent of the radial labeled dose

recovered as apparent compound in the urine.

The primary metabolic pathway is hydroxylation on the indole ring followed by glucuronide or sulfate conjugation. The mean elimination half-life in normal adult volunteers, age 19 to 40 years old, is 3 and a half hours.

The labeled indications for IV ondansetron are the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy and the prevention of post-operative nausea and vomiting.

This slide provides the recent regulatory history related to the 32-milligram single IV ondansetron dose. In September 2011, the FDA issued a drug safety communication, which stated that Zofran and generic ondansetron products may increase the risk of cardiac arrhythmias such as QT prolongation, which could be serious and lead to a sometimes fatal heart rhythm called Torsades de Pointes. Because of this concern, the FDA required the applicant holder to conduct a thorough QT trial to further assess this risk.

In June 2012, the FDA issued another drug safety communication which discussed the preliminary results of the thorough QT trial. The trial suggested that a 32-milligram single IV ondansetron dose could prolong the QT interval.

This slide shows the results of the thorough QT trial. The trial design was a double-blind, single-IV dose, placebo- and positive-controlled, crossover trial that was conducted in 58 healthy subjects. The study demonstrated that ondansetron prolonged the QT interval in a dose-dependent manner.

The maximum mean difference in QTcF from placebo after baseline correction was 19.5 milliseconds after a 15-minute IV infusion of ondansetron 32 milligrams and 5.6 milliseconds after a 15-minute IV infusion of ondansetron 8 milligrams.

The data demonstrated that the 32 milligrams single IV dose significantly prolonged the QT interval. Additional analysis of the data were useful in determining the maximum safe and

effective dosing for the ondansetron IV formulation.

Based on the results of the thorough QT trial, in November 2012, the professional labeling for Zofran was changed to remove the recommendation for a 32-milligram single IV dose and to add statements that ondansetron IV could continue to be used in adults and children for the prevention of chemotherapy-induced nausea and vomiting at a lower IV dose. However, no single IV dose should exceed 16 milligrams.

A month later, in December 2012, the FDA issued another drug safety communication which notified healthcare professionals that the 32-milligram single IV ondansetron dose would no longer be marketed because of the potential for serious cardiac risk.

Based on the potential of the 32-milligram single IV dose of ondansetron to prolong the QT interval, the FDA determined the single 32-milligram IV dose was withdrawn for reasons of safety.

In summary, the FDA recommended entry for the withdrawal or removal list for ondansetron hydrochloride as all intravenous drug products containing greater than a 16-milligram single dose of ondansetron hydrochloride.

The rationale for the determination by the agency is based on analysis of the thorough QT trial data, which demonstrated that the risk of QT prolongation is greater with a 32-milligram single IV ondansetron dose compared to the single IV ondansetron doses of less than or equal to 16 milligrams.

Data analysis demonstrated that the lower single doses of less than or equal to 16 milligrams IV ondansetron are safe and effective for the prevention of CINV in adults and children compared to the safety profile of the 32-milligram single IV dose and no single IV dose should exceed 16 milligrams.

Although a dosing change was made to ondansetron, oral formulations of ondansetron were reviewed and were expected to lead to lower maximum

levels of the drug in the blood stream compared to the IV administration. Therefore, no dosing changes were recommended. This concludes my presentation.

Clarifying Questions from the Committee

DR. VENITZ: Thank you, Dr. Berry.

Any clarifying questions? I have a question on your slide number 5, when you introduced the thorough QTc study and you referred to preliminary results. What does that mean, preliminary results? You're presenting to us the final results, right?

DR. BERRY: Right. I presented the final results. We submitted -- we sent out a drug safety communication once we got that information to let the people know.

DR. VENITZ: In that year? In that particular year, right? On your next slide, those are the final results, right?

DR. BERRY: Those are the final results, correct.

DR. VENITZ: Okay. Thank you. Mr. Mixon?

MR. MIXON: Thank you. A similar question

on the last discussion, is there any evidence that people are ignoring the warnings in the literature and are compounding doses greater than 16 milligrams?

MS. AXELRAD: I have to give the same answer. We don't know what people are compounding because we have no way to know. As I said, we're putting the drugs on the list or recommending that they be put on the list if we have found that they've been removed from the market because they're unsafe. And we want to put the list out there, and if people are not compounding it, great. And if they are, they should look at the list and make sure that they're no longer doing it.

MR. MIXON: Thank you.

DR. VENITZ: Dr. Braunstein?

DR. BRAUNSTEIN: I assume that this would somehow also prevent the compounding of a multi-unit, multi-dose file, right? Is that the intent here, that Zofran or ondansetron would only be compounded as single unit for intravenous? I'm curious about how this would be -- of the actual

implication of this from a practical point of view.

MS. AXELRAD: I think Dr. Korvick --

DR. BERRY: Again, it's not clear to us if it's being compounded and at what dose it's being compounded. But our concern was to make sure that people knew that that 32-milligram dose, which had been in the label for adults for the prevention of CINV, that there were safety issues related to that and it should not be used. I think Dr. Korvick may have some other comments.

DR. KORVICK: Yes. I would like to also add that when you looked across the products as they were packaged and supplied, there was a single-use product that was greater than 16 milligrams. Because of the safety, that was really our thrust.

I think if there was clearly marketed, a multi-use preparation, that would be a different matter as long as you followed the labeling. So we're talking about the preparation in that regard, is the single-use, single dose.

DR. VENITZ: Can you just identify again for the record?

DR. KORVICK: I'm sorry. I'm Dr. Korvick. I'm the deputy director for safety for the Division of Gastroenterology and Inborn Errors Products.

DR. VENITZ: Thank you. Any other clarifying questions? Mr. Mixon? Sorry. Dr. Wall?

DR. WALL: To answer Bill's question, when asked around, there are some 24's being compounded in highly emetogenic chemotherapy patients.

DR. VENITZ: Mr. Mixon?

MR. MIXON: So how is a pharmacist to respond to an order for a continuous infusion of ondansetron for somebody with severe emesis?

MS. AXELRAD: I don't know how to answer that question. Maybe someone else on the committee would like to talk about this. I mean, we're saying you shouldn't compound it so that it would be given in a single dose of over 16 milligrams. I don't know how you would interpret that.

MR. MIXON: Does anybody on the committee have any experience with continuous IV infusion on this drug? I can certainly imagine that the

circumstances would arise where the patient would need some sort of emetogenic -- anti-emetogenic drug.

MS. DAVIDSON: I do in nonhumans, but that's not relevant here. I wanted to follow up on Donna's question and maybe yours. I noticed in the briefing material, there was description of the fact that there's no evidence for the effects on QT interval prolongation for doses of 24 milligrams. And if people are compounding 24 milligrams, the question I have is, why did you decide 16 and not 24?

DR. BERRY: That's a good question. Thank you. During the further analysis, we were able to use modeling of pharmacokinetic data and pharmacodynamic data in addition with clinical data to help us determine that that 16 milligram dose was the dose.

Anything less, 16 or less, was the dose where we didn't see that -- where we wouldn't have that prolongation of the QT interval. That's why you see the 16 milligram dose there. That's based

on pharmacodynamic and pharmacokinetic data modeling.

DR. VENITZ: Dr. Gulur?

DR. GULUR: I'd just like to respond to the continuous infusion question that you had. It's normally not common to have doses as high as 32 milligrams in a continuous infusion. They usually run at lower dose in the protocols that are commonly followed.

The other thing is when the continuous infusions are run, another part of the protocol -- and I can't assure that this is what happens everywhere, but in most places QTc monitoring does occur in the initial periods to ensure that they are not at risk with it.

MR. MIXON: I think the committee needs to consider some sort of dose over time rather than just categorizing or categorically saying that you can't have more than 16 milligrams in a continuous infusion. I mean, what if the patient is at home in their own home IV therapy, and their only means of controlling their nausea is a continuous

infusion of Zofran?

What's the pharmacist to do if they need a 5-day or a 7-day supply that runs at a very low rate? I mean clearly, you're not going to be given 32 milligrams per dosage interval, but it's problematic when it comes to compounding the drug for home infusion or even in a hospital setting.

I think that -- obviously, 32 milligrams as a bolus over a 15-minute period is going to pose significant danger but 32 milligrams that's going to be infused over five days is not. I think that needs to be considered.

DR. VENITZ: Go ahead.

DR. KORVICK: Dr. Korvick from the Division of Gastroenterology and Inborn Errors Products. I just want to say that our labeling, as it's approved, doesn't have any data. We have not been submitted on continuous infusion dosing.

DR. VENITZ: Thank you.

MS. AXELRAD: And the compounded products don't have any labeling at all other than what's in it, hopefully.

DR. VENITZ: Dr. Vaida?

DR. VAIDA: This reminds me of the last meeting with the esmolol, the 250-milligram per mL. With this, we're talking about a 32-milligram single intravenous dose. I know a 503A, and especially in 503B, a lot of them make a living on compounding concentrations that aren't available commercially. I would look at this as the 32-milligram intravenous bolus, I mean, was removed from the market.

So that's what we're looking at. We're not looking at making a continuous infusion or -- I'm not even aware that it's given by continuous infusion although I haven't practiced in the hospital for a couple of years but I do visit a lot of hospitals, especially oncology hospitals. I mean I think this is just like the esmolol one that we talked about at the last meeting.

MR. MIXON: But it's subject to interpretation, and many regulatory agencies, besides you and me and the FDA, are going to be looking at interpreting the rules that are made

here today.

DR. VENITZ: Dr. Jungman?

MS. JUNGMAN: If there were a patient need for a continuous infusion, would there be an FDA-approved version of the product that would be useable in that circumstance?

MS. AXELRAD: I believe, yes. This is applicable to this specific dose. Correct, Joyce?

DR. KORVICK: Yes. I think the products approved as it's approved, the certain intravenous concentrations that are marketed -- I don't know how you would use that information to do continuous infusion. I mean, you've got a quality intravenous drug that's been approved by the FDA, but I don't know how to answer your question any further.

MS. AXELRAD: So did that answer your question? There are FDA-approved products available, correct?

(Dr. Korvick nods affirmatively.)

MS. JUNGMAN: Yes, that answers my question. I think what we're trying to get at, the version of the product that would need to be compounded and as

the version has been removed from the market, if there's a need for a continuous infusion, it seems like there are other FDA-approved alternatives available.

DR. VENITZ: Thank you. Okay. Last question, Dr. Hoag?

DR. HOAG: Quick thing. When I looked at the label, I was kind of surprised to see that the dose, it's cited in the label that you handed out in your handout is based on the ondansetron hydrochloride dihydrate. But you go to the USP and they say "ondansetron." So there's like a 20 percent difference in the molecular weights. Would you say the dose that you want to control -- I think most people do like the base, but anyway, that should be clearly defined what exactly -- because someone has to weigh that out, so that should be added to the language of what you're saying.

DR. BERRY: Thank you.

DR. VENITZ: Thank you. Yes, Dr. Davidson, final, final question.

MS. DAVIDSON: Just a point of clarification, and it may be a point of misunderstanding for many pharmacists. The Do Not Compound list -- I know we call it other things now -- but the Do Not Compound list has historically been interpreted as a list of bulk substances for which you should not use to compound by pharmacists -- wouldn't you agree with that, Bill -- and not applied to commercially available, FDA-approved products?

Is that correct or is the interpretation now that I cannot draw up 16 mLs of ondansetron, 2 milligram per mL in a syringe to dispense to patients for multiple use?

MS. AXELRAD: I think if you go back to the original list that's been out there in the codified for a while, as well as the drugs that we talked about at the last meeting, it isn't just only drug substances. For some of them, they are drug substances, but in other cases, there are qualifications with regard to dosage for a route of administration and use. We qualified one with

regard to ophthalmic use. So it isn't, across the board, only the drug substance.

Also, just to clarify, we all shorthand it by saying the "Do Not Compound list." And what it is, is the list of drugs that cannot be compounded by someone who wants to qualify for the exemptions under Section 503A or 503B.

DR. VENITZ: Okay. Thank you. Thank you, Dr. Berry. Let's move on to our last compound for this morning, bromocriptine. And we now have Dr. Christine Nguyen -- she's a deputy director for safety within the Division of Bone, Reproductive, and Urological Products -- to present the recommendation.

Presentation – Christine Nguyen

DR. NGUYEN: Good morning. I'm Christine Nguyen, and I am from the Division of Bone, Reproductive, and Urologic Products in CDER. This morning, I'll be giving a brief presentation on Parlodel and the removal of its indication of lactation suppression for reasons of safety.

In my presentation, I will describe

Parlodel, its regulatory history, outline the major safety concerns with its use for lactation suppression, and lastly, I'll provide an overview of FDA's determination and action leading to the withdrawal of its indication of the prevention of physiological lactation.

Parlodel is an ergot derivative with potent dopamine receptor agonist activity that inhibits prolactin secretion. Because prolactin is necessary for human lactation, its inhibition prevents physiological lactation in women when the drug is started after delivery and is continued for two to three weeks postpartum.

Parlodel was initially approved in 1978, and two years later, it received approval for the indication of the prevention of physiological lactation. This drug is currently marketed and has approved indications, and these include hyperprolactinemia associated dysfunctions, acromegaly, and Parkinson's disease.

Soon after its 1980 approval for lactation suppression, FDA began receiving postmarketing

cases of serious adverse outcomes and even deaths associated with the use of Parlodel for lactation suppression in mostly otherwise healthy postpartum women. These reports included severe hypotension, seizures, strokes, and myocardial infarction. And by 1989, FDA had received 85 postmarketing reports of such serious adverse outcomes, including 10 deaths.

FDA presented safety concerns at the 1989 advisory committee for Fertility and Maternal Health Drugs. The AC panel ultimately recommended no drug label for lactation suppression, including bromocriptine, or Parlodel, be used for this indication.

FDA followed the AC's recommendation, and after that meeting, it asked that all manufacturers of drugs containing bromocriptine to voluntarily remove the indication because of the serious risk that I outlined outweigh the products marginal benefit in preventing postpartum lactation.

All manufacturers comply with FDA's request except for the manufacturer of Parlodel.

Subsequently, FDA published a notice in the Federal Register on January 17, 1995 announcing the withdrawal of Parlodel's indication for the prevention of physiological lactation for reasons of safety. The withdrawal became effective on February 16th, 1995.

The rationale for FDA's determination and action is that lactation is a self-limiting condition. The ability to lactate disappears if a woman does not breastfeed, and this usually happens within 7 days postpartum.

Breast engorgement and its discomfort prior to the complete suppression of lactation is a non-serious condition. These symptoms may be adequately treated with non-pharmacologic measures such as breast binding and also with mild analgesics.

Given the reports of serious adverse outcomes when used for lactation suppression, including deaths, FDA determined that there was an unacceptable benefit/risk balance for this indication. Thank you.

Clarifying Questions from the Committee

DR. VENITZ: Thank you, Dr. Nguyen. Any questions? Dr. Braunstein?

DR. BRAUNSTEIN: So I just want to understand something. I have a license to practice medicine. First of all, I have a license to practice medicine in the State of New York, and I agree with all the scientific things that you stated. But I believe that if I chose to, I could legally prescribe Parlodel to a patient to -- I mean it would be -- aside from the fact that I think it would be terrible medicine. But just for the point of -- I'm just talking now about regulatory authority, all right. So I want to think about this in that context.

All right. I could, I believe, legally prescribe the drug for this indication. Is that -- I think we would all agree to that?

DR. NGUYEN: I'll take it from the least perspective of the general policy of FDA regulating, rather not regulating the practice medicine.

DR. BRAUNSTEIN: You couldn't regulate the practice of medicine, right. So I'm not sure if you're treading on a line here. The drug is available, right, and it's made available in this way. Yet you're regulating my use of the product, perhaps, in a way that I'm not sure the law allows.

I'm asking this, you know -- and I'm taking the approach now just from the perspective of where the regulatory line is in terms of what can or can't be done. So I'm going to put that out there.

MS. AXELRAD: So what we're looking at here are the conditions under which a drug can be compounded under 503A or 503B. The statute directs us to identify a list of drugs that cannot be compounded in accordance and still qualify for the exemptions under 503A and 503B if they'd been withdrawn or removed from the market because they'd been found to be unsafe or ineffective.

We're developing that list, and we have, in the past, in the original list that we put out, as well as in the 25 or so drugs that you voted on the last time, we have said that if it needs to be

certain -- if there'd been qualifications on it, that you can't compound it under those circumstances.

All we can do is identify the things that have been withdrawn or removed from the market because they've been found to be unsafe and ineffective and put them on a list.

As was indicated, we're not trying to regulate the practice of medicine. A doctor can prescribe a drug for an off-label use, but we can't -- you know, a compounder cannot compound it if it's on the list for this particular use.

DR. NGUYEN: And I'd like to add that I think that's distinct from using an approved drug off-label.

DR. VENITZ: Dr. Davidson?

MS. DAVIDSON: I was just going to agree that it is widely available as an approved product, and a pharmacist ordinarily wouldn't question a prescription for an approved product except for the reasons you stated, that it may not be good medicine, but they're not going to challenge your

judgment on that. So there probably would be no need to compound this, is my point.

DR. VENITZ: Dr. Jungman?

MS. JUNGMAN: That's really what I was trying to confirm. My understanding is that for the approved uses, you wouldn't need to compound it because then you couldn't compound it because there is a commercially-available product.

Then for this additional use, the lactation suppression use, that's really what we're deciding or we're making a recommendation here today. Ultimately, if FDA decided to put this particular use on the withdrawn or removed list, as I understand it, you just wouldn't be able to compound this product at all.

MS. AXELRAD: Well, I think you could compound it for the other uses. Like you can take the FDA-approved product, and if you need a different dosage form or something like that for one of the uses, it is on the label then; a compounder can compound it --

MS. JUNGMAN: But you have to start with the

FDA-approved product; you couldn't start from bulk.

MS. AXELRAD: Yes, well, we're not talking about the bulks list here anyway. We're on the withdrawn or removed list. Under the bulks list under the 503A, since it is the bulk drug substances, in fact a compound of an FDA-approved drug, then you can compound from the bulk under the 503A bulk list, period. What we're saying is that you can't compound it if you know that it's going to be used for this particular indication.

MS. JUNGMAN: How does the essentially copy provision then plan?

MS. AXELRAD: Well, that's a totally -- okay. So that would be you cannot, under 503A, copy regularly or inordinate amounts what's essentially a copy of an FDA-approved product.

I don't know enough about this. But let's say the drug is available 10 milligrams oral, and somebody can't take a pill, so you're going to make a liquid. That would probably not be essentially a copy of an FDA-approved product. As long as you

weren't doing it regularly or in inordinate amounts, it would fine if it were a copy.

MS. JUNGMAN: Thank you.

DR. VENITZ: Any other clarifying questions? Yes, Dr. DiGiovanna?

DR. DiGIOVANNA: Can I ask a qualifying question about an earlier presentation?

DR. VENITZ: Go ahead.

DR. DiGIOVANNA: With respect to the aprotinin, where I had asked the question of there was an open-label study that was apparently done to permit certain subgroups of patients. A quick comment.

Apparently, there's an article that was published in May in PLOS ONE that comes from Boston Children's Hospital in Harvard Medical School that studied over 550 patients who had anti-fibrinolytic therapy for neonatal cardiac surgery, and mentions in my brief look at the introduction that it had been withdrawn by, I guess it's BART. And their conclusion is that it's safe and effective.

We didn't hear about anything positive about

that. The only thing we heard of was the negative issues. So I'm a little surprised we didn't hear of that very recent study, which it appears was done in response to the fact that it was taken off of the market.

So again, I guess it raises the concern, is our goal to remove everything, put everything on the withdrawn list that has had some negative experience, and are there subgroups of population who are going to be placed at some sort of risk because they're going to become unavailable?

DR. VENITZ: Can we hold that question for discussion? Because right now, we're just trying to get clarifying --

DR. DiGIOVANNA: Okay.

DR. VENITZ: I didn't realize how extensive your clarifying question was going to be.

Any other clarifying questions to Dr. Nguyen's presentation?

(No response.)

DR. VENITZ: Okay, then. Thank you very much, Dr. Nguyen. So this concludes our formal

presentation section. We will now take our first break.

Committee members, please remember that there should be no discussion of the meeting topics during the break among yourselves or with any member of the audience. Please return to your seats at 11:00 a.m., at which time we will convene the first open public hearing session. Thank you.

(Whereupon, at 10:30 a.m., a recess was taken.)

Committee Discussion and Vote

DR. VENITZ: Let's reconvene please.

Now, this time was supposed to be open public hearing, but since we don't have any registrants for our first OPH session, we will now move on to the committee discussion and voting. I'm proposing that we do that by compounds, so we're going to start off with acetaminophen.

The idea here is for the committee to discuss the recommendation that was put in front of us, and then ultimately be ready to vote. Okay. So we have them in different order. I take that

back. You look at the screen in front of you. The first drug we're going to talk about is aprotinin. We're going a little off the sequence that we had the presentations.

Our first drug is aprotinin. I'll open the discussion, and Dr. Axelrad wanted to make some comments.

MS. AXELRAD: I just wanted to address Dr. DiGiovanna's question about that. Generally, once we take a drug off the market or we make a determination that a drug is unsafe, either totally unsafe or unsafe for a particular use or dosage form or route, we would not change that unless the sponsor asked us to do that.

We would expect that if somebody, anybody, the sponsor or anybody else, was going to be doing a study of it in anyone for that particular use, that they would be doing that under an IND. So the mechanism is either it's under a new drug application, an approved new drug application, or it's done under an IND. Once it's been taken off the market with regard to the labeling from a new

drug application, the way to look at it is under an IND.

With regard to the specific study that you saw, we did a very quick look at it right now. First of all, it was very recent; it was in May. Dr. Suh can probably just mention what she noticed on a quick glance at that.

DR. ROBIE SUH: Let me just say just generally, looking at publications, those are not the same as looking at studies that have been conducted under an IND and submitted data-wise to the agency. I think this one was observational also, a retrospective look at patients.

Then I can also say that for applications, typically, the way we look at the literature is within the annual reports submitted for all of our applications. Every year, we look to see if anything has been reported, occurred, or whatever would change our findings about the drugs. That's usually the way we handle that.

MS. AXELRAD: We obviously can't talk in an advisory committee about whatever might be going on

with an application, an existing application or obviously an IND. We can't talk about that publicly here.

I think Dr. Suh was talking sort of generically that if there is new information that becomes available, it may be submitted in a sponsor's annual report, for example, or there are updates provided to us, or there could be studies. You can look on clinicaltrials.gov; if they're being done under an IND, they're supposed to be listed there.

DR. VENITZ: Any discussion, any comments? Dr. DiGiovanna?

DR. DiGIOVANNA: The question to us is, do we add this to the list? If we're going to add it now, then it would seem to me that it would be reasonable to have what's been published about it, that isn't from an IND -- because it's now on the list now. Is that correct? We're being asked to add it --

MS. AXELRAD: The drug was withdrawn or removed from the market for safety reasons, and

we've articulated the basis for why that drug was withdrawn or removed from the market for safety reasons.

Once that is the case, the way to reverse that, if you will, would be for a sponsor to submit data that shows that the drug is, in fact, safe and effective for the use. It isn't appropriate to just look in the literature and see whether -- we're really looking at whether the drug was, in the past, withdrawn or removed for safety reasons. And before it can be reversed, that ought to come to the agency in terms of safety and efficacy data to show that it's safe and effective.

You can't just have somebody publish an article and then decide that regardless of the fact that we did that, you can just go ahead and use it. In fact, the manufacturer couldn't do that. They couldn't just say, oh, well, here's an article I read in a magazine. Now, I can promote my drug for this use because there was a study done that showed -- also, my understanding is that from a

quick look at this, this was a chart review. Is that correct? You raised it; we just looked it up. But it was a chart review. It wasn't a study that --

DR. ROBIE SUH: Not what we would call an adequate and well-controlled study that would rise to the level that the agency would independently go out and seek the results of this study to inform the product label.

DR. HERTZ: This is Sharon Hertz. I just want to put this in context. When a finding that a drug has a safety concern, sufficient so that the risks outweigh the benefits and it's withdrawn, that's a determination that's based on a number of factors.

If there is, in the future, a determination that there's a population that could benefit from the drug in a different setting, there is always opportunity to initiate investigations to explore that use. The prior withdrawal or the listing on the no compounding list do not, in any way, interfere with that.

So I think that if we looked overall at the literature for any of these products, we'll see a variety of studies that describe both favorable and unfavorable outcomes. I think it's important that you pointed out that one study. We'll certainly look at it more. But I don't think that negates the available information that overall has determined the status of this product with regard to its overall safety and efficacy.

The current question of putting it on the compounding list, I'm not sure that, really, a retrospective chart review or other type of study like that in isolation should be interpreted to outbalance a variety of sources of information. But it is something that we'll look into as it's relevant and if it comes up for that population that they decide there is a need.

DR. VENITZ: Dr. Carome?

DR. CAROME: I'm Mike Carome, Public Citizen. Generally, I completely agree with the position and the recommendations made by FDA for these four drugs. From a patient safety and public

health standpoint, these drugs have been removed from the market for safety and/or evidence that they're not effective.

503A and 503B create loopholes in the Food, Drug, and Cosmetic Act for approval of drugs which are intended to ensure that drugs are safe and effective. Once these have been removed from the market, the burden of proof can bring them back needs to be high, and we shouldn't allow loopholes and have compounders make them and bypass those rules, which are intended to protect patients.

So I strongly endorse, including all of these on the list. I think FDA's thought process is very good.

DR. VENITZ: Dr. Pham?

DR. PHAM: Just speaking from the in-patient children's institution, it has actually come up, even at Children's National, at least twice in the past four years, and we were able to get it for our patients under the IND.

DR. VENITZ: Dr. Gulur?

DR. GULUR: I just wanted to complete the

thought. If I understand correctly, we haven't looked at data since the drug was removed, any publications since the time, and that would mean a few years at this point of data that needs to be looked at.

This study is, of course, very recent, 2015. There are other retrospective studies from Levy in 2011, which actually showed that aprotinin was actually causing AKI in neonates as well. So it would require a full systematic review of data from that time, and I would also agree that that's the way to approach it as opposed to relying on just a few studies.

MS. AXELRAD: And I would just say that's usually done by a sponsor who wants to get it either back on their label or approved somehow for that use.

DR. VENITZ: Dr. DiGiovanna?

DR. DiGIOVANNA: I just would like one clarification. It seems that if a drug has been withdrawn from the market, it automatically goes on the list?

MS. AXELRAD: Well, we look at the data, and we have to articulate, we have to do it by rulemaking. We do a review of the data, and we articulate why it was withdrawn from the market for safety or efficacy reasons. And that's what you see in the reviews that you got.

Obviously, it's not automatic because we have a process to go through; we have to propose it, and we're required to consult with the advisory committee. I would sort of hate to think that it's automatic because we wouldn't be needing to do any of that if it was totally automatic. So we are trying to do a thoughtful review.

As I said, and I think Dr. Gulur also said, in order to reverse something that was done in the past, one would have to do a very systematic look at the data that have been generated since then to see whether there's anything that would suggest that it should be change.

Generally, those reviews are done by the sponsor, and they would go through the drug approval process in order to get the labeling

changed or something like that.

DR. VENITZ: Dr. Jungman?

MS. JUNGMAN: Just to add to that, and this may be old news to you, but FDA isn't always going to know why a product was withdrawn or removed for the market. So I think the inquiry is really looking at do we have enough evidence to suggest this was removed for safety and effectiveness reasons or could it have been a business decision or something like that.

DR. VENITZ: Dr. Carome?

DR. CAROME: I'm Mike Carome. There are multiple examples of drugs that had been removed from the market for which FDA has declared it was not removed because of a safety or efficacy concern, and those won't go on this list. So it's not that every drug that's removed goes on the list, but just those for which there's evidence that it was unsafe or not effective.

DR. VENITZ: Any further discussion or comments before I call for the vote? Yes, Dr. Hoag?

DR. HOAG: Steve Hoag. I was just going to say that the first drug there could probably also go on tomorrow's list. If I looked at how hard that would be to formulate in a stable thing that wouldn't precipitate the tools available to a compounding pharmacist, it would make me very nervous about trying to compound that product.

DR. VENITZ: Thank you. Any further comments?

(No response.)

Okay. Then let's proceed unless somebody violently opposes with our vote.

Let me read you the instructions. They are very similar to what we did last time. 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 your selection firmly three times. After everyone has voted, the vote will be complete.

The first vote that we have is, if you look at the screen in front of you, is number 1, FDA is

proposing that aprotinin, all drugs products containing aprotinin, be added to the withdrawn and removed list. The question you're voting on is, do you agree; yes, no or abstain? So please go ahead and push the button.

(Vote taken.)

DR. VENITZ: Okay. So our final vote is we've got 10 yes, zero no, and 1 abstain. So it looks like we have almost unanimous vote in favor of the FDA recommendation. Any comments, final comments?

(No response.)

DR. VENITZ: Okay. Then let's move on to our next compound of interest, and that's ondansetron, if I've got that written down correctly. Any comments, any discussion items regarding FDA's recommendation to remove ondansetron from the compounding list?

Yes, number 2 is ondansetron. Any comments?

(No response.)

DR. VENITZ: Okay. Are you already for the vote, then? Okay. Then let me read the

instructions again. Each voting member has three voting buttons on your microphone: yes, no and abstain. Please vote by pressing your selection firmly three times. After everyone has voted, the vote will be complete. Please go ahead and press your button.

You're voting on FDA's proposing that ondansetron hydrochloride, all intravenous drug products containing greater than 10 milligrams single dose of ondansetron hydrochloride, be added to the withdrawn or removed list. Do you agree; yes, no or abstain?

(Vote taken.)

Okay. Our final vote is we've got 11 yes, zero no, zero abstains, so we have a unanimous support for FDA's recommendation. Any comments?

(No response.)

DR. VENITZ: Okay. Thank you. Then let's move on to the third compound that we have bromocriptine. Again, discussion items, comments?

(No response.)

DR. VENITZ: Is everybody ready for the

vote? Okay. Then same voting procedures, you've got three buttons; yes, no, abstain. Please vote by pressing your selection firmly three times. We have two individuals, Dr. Vaida and Dr. Humphrey, that cannot vote. So everybody but those two individuals please press yes, no or abstain.

(Vote taken.)

Okay. We have our final vote count. We've got 9 yes, zero no, and 1 abstention, and 1 no vote.

Is that the way it's supposed to -- so should we revote? Yes. Let's revote, then.

Okay. Let's discard the current count, and let's revote on question number 3. So we are voting on FDA's proposing bromocriptine mesylate, all drug products containing bromocriptine mesylate for prevention of physiologic lactation be added to the withdrawn or removed list. Do you agree? Please press yes, no, or abstain.

(Pause.)

DR. VENITZ: It's not blinking. We have to reset it. Okay. Now press the button, please.

(Pause.)

DR. VENITZ: We have to reset the voting system, whatever that means. That means we have to do it again. The third time is a charm. So hold on until we get the okay that everything is reset.

(Pause.)

DR. VENITZ: Okay. So we're voting on question number 3, bromocriptine mesylate. Do you agree with FDA's recommendation as outlined on the screen in front of you? Yes, no, abstain, please?

(Vote taken.)

DR. VENITZ: Okay. Now, we have our final vote count, yes, 9; zero no; zero abstains; and 2 no votes, which is what it's supposed to be. Any final comments on bromocriptine?

(No response.)

DR. VENITZ: Okay. Then the last compound for this morning is acetaminophen. Any further discussion of acetaminophen?

MS. AXELRAD: Dr. Venitz?

DR. VENITZ: Yes.

MS. AXELRAD: I think we'd like to just

clarify our answer to an earlier question about whether this is limited to prescription or not. I'm going to turn to Dr. Hertz.

DR. VENITZ: Go ahead.

DR. HERTZ: So the actions that we've taken so far, that I mentioned regarding the process in the FR notice, has been for the prescription products. The OTC products are following -- or any product under an NDA, the OTC monograph products have a different process that's being pursued, and this recommendation that we've made is for all products.

MS. AXELRAD: It applies to both prescription and over-the-counter compounding of dosage units containing more than 325 milligrams. Basically, the regulatory processes are different for NDA or ANDA products than they are for monograph products, where you need to go through a rulemaking, I believe, to do what you need to do.

But the policy that we've described and the science behind it applies the same to both prescription and over-the-counter drugs. So we

would not be qualifying this to say all prescription drugs containing more than -- it would read the way we've written it, which is all drug products containing more than 325 milligrams of acetaminophen per dosage unit.

DR. VENITZ: So the intent would be that all Tylenol products, prescription or over-the-counter, will have to follow --

MS. AXELRAD: Yes. We would just leave it at "all" because "all" means all.

DR. VENITZ: Okay. Dr. Pham?

DR. PHAM: I had a comment that would have pertained if this had meant all drug products. Just from a pediatric perspective, when it was prescription products and it's usually combination, usually, it's the other ingredient that is guiding the dosing of that combination product.

When it's acetaminophen over-the-counter, just as a caveat, 10 milligrams per kilogram is the standard pediatric dose, so that means a 50-kilogram child already goes to 500 milligrams. A lot of times, we end up having to round. We use

the liquid product that's commercially available over-the-counter, and that ends up being a very large volume for some of these pediatrics patients.

Just a consideration, that was just a comment that I had reserved when I thought that we were all voting on all prescription drug products, but this would probably then assume a larger use and larger volumes, the oral, commercially available oral solution.

DR. VENITZ: Any additional comments? Yes, Dr. Wall?

DR. WALL: Just to piggy back on that, I keep thinking if you buy acetaminophen liquid in 4-ounce bottles, so what does that mean? Are we just saying a change in the labeling that says a dose is only 325 or -- I'm not sure how that applies to that picture right now, I guess.

DR. HERTZ: What we're saying is that for the purposes of compounding, our policy is consistent with the actions that have so far been completed but that are underway for other products. And that is, for the reasons described, we've

concluded that single dosage units above 325 should not be either approved or compounded. So that's what we're recommending.

If there are clinical considerations in which a prescriber chooses to alter a dose for individual patients, for instance, between a physician and a patient, they could say, take three 325-milligram tablets for this reason in a one-on-one conversation, that's practice of medicine.

If a clinician needs a particular amount of medication for a situation, that's not what we're saying. We're saying that products should not contain more than 325 per dosage unit, and then how dosing is achieved for a therapeutic goal should be within that context.

MS. AXELRAD: I think you were raising a question like if you have a liquid, you have a bottle that has whatever concentration in it, that's the dosage -- I mean the question is, is that the dosage unit? If you have a liquid, the label would say, do this much, which would mean the

dose would be less than 325 milligrams or less. And presumably for a child, it would be significantly less.

But is that the question, really, is if you're talking about a bottle, is the unit -- what does this translate into?

DR. PHAM: No. It was just more that when you're dealing with doses -- there's actually quite a large weight population in pediatrics that will have a dose in between 325 and 650. I don't know if the 500s were already withdrawn because we actually haven't been carrying them on our formulary anyway.

But a lot of times, you have a dose of like 510, and you think dosing -- changing it to 650 is too much of a jump, and 325 is not enough, so you don't have the 500-milligram option. You end up giving the liquid just to keep it as close as possible and ends up being something like 160 per 5.

So it's just like a 20-amount, like it's just a large dose, that a patient that could've

swallowed a tablet will end up taking by volume, by liquid.

DR. VENITZ: Dr. Wall?

DR. WALL: Mine was more along the lines of the bottling because pharmacists are so precise in things as to look at what is a dosage unit. And you will have some who will say, well, is the dosage unit going to be just what a dose is labeled on the bottle? I think it's more my question --

DR. HERTZ: A dosage unit would be, for instance, if the intended concentration is 325 milligrams per 15 mL, the 15 mL is the dosage unit in that setting. If the intended volume for the dosage unit is 5 mL, 325 per 5 mL, that would be the dosage unit in that setting.

DR. WALL: So it's the dosage unit that's based on the 325?

DR. HERTZ: What we're saying is that whatever the intended dosage unit is -- so if somebody needs to compound a liquid and they choose to use a 15-milliliter dosage unit for the patient because that's the appropriate volume for that

patient, it should be no more than 325 in that dosage unit.

DR. VENITZ: Yes, Mr. Mixon?

MR. MIXON: What will become of the status of acetaminophen 650-milligram rectal suppositories that are commercially available?

DR. HERTZ: The OTC process is currently underway to make changes consistent with what we've described.

MR. MIXON: I'd like to have a nickel for every one of those that I've dispensed; I'd be rich.

DR. VENITZ: Any other comments?

(No response.)

DR. VENITZ: Okay. Then let's move to our last vote this morning. We're now voting on question number 4. FDA is proposing that acetaminophen, all drugs products containing more than 325 milligrams of acetaminophen per dosage unit be added to the withdrawn or removed list. Do you agree? Please press yes, no, or abstain.

(Vote taken.)

Adjournment

DR. VENITZ: Okay. We have our final vote: 10 yes; zero no; and 1 abstain, so again, a large majority in favor of FDA's recommendation. Unless there are any other questions or comments, this would conclude our morning session. We'll now take an early lunch break.

I was just informed we cannot reconvene until 1:10, so you have a long break. No nap, please. Try to be back at 1:10, and we'll reconvene our afternoon session. Thank you.

(Whereupon, at 11:30 a.m., the morning session was adjourned.)