FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACY COMPOUNDING ADVISORY COMMITTEE

(PCAC)

Wednesday, March 9, 2016

8:30 a.m. to 10:02 a.m.

FDA White Oak Campus

10903 New Hampshire Avenue

Building 31 Conference Center

The Great Room (Rm. 1503)

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Cindy Hong, PharmD

Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

PHARMACY COMPOUNDING ADVISORY COMMITTEE MEMBERS (Voting)

Michael A. Carome, MD, FASHP

(Consumer Representative)

Director of Health Research Group

Public Citizen

Washington, District of Columbia

Gigi S. Davidson, BSPh, DICVP

U.S. Pharmacopeial Convention

(USP) Representative

Director of Clinical Pharmacy Services

North Carolina State University

College of Veterinary Medicine

Raleigh, North Carolina

John J. DiGiovanna, MD
Staff Clinician, DNA Repair Section
Dermatology Branch, Center for Cancer Research
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

Padma Gulur, MD
(Acting Chairperson)
Professor, Department of Anesthesiology and
Perioperative Care
University of California, Irvine
Orange, California

Stephen W. Hoag, PhD
Professor
Department of Pharmaceutical Science
University of Maryland, Baltimore
Baltimore, Maryland

William A. Humphrey, BSPharm, MBA, MS
Director of Pharmacy Operations
St. Jude's Children's Research Hospital
Memphis, Tennessee

Elizabeth Jungman, JD
Director, Public Health Programs
The Pew Charitable Trusts
Washington, District of Columbia

Katherine Pham, PharmD
Neonatal Intensive Care Unit Pharmacy Specialist
Children's National Medical Center
Washington, District of Columbia

Allen J. Vaida, BSc, PharmD, FASHP
Executive Vice President
Institute for Safe Medication Practices
Horsham, Pennsylvania

Donna Wall, PharmD

National Association of Boards of Pharmacy (NABP) Representative

Clinical Pharmacist

Indiana University Hospital

Indianapolis, Indiana

PHARMACY COMPOUNDING ADVISORY COMMITTEE INDUSTRY REPRESENTATIVE MEMBERS (Non-Voting)

Ned S. Braunstein, MD

(Participation in March 8th PM session and March 9th session)

Senior Vice President and Head of Regulatory Affairs

Regeneron Pharmaceuticals, Inc.

Tarrytown, New York

William Mixon, RPh, MS, FIACP

Owner-Manager

The Compounding Pharmacy

Hickory, North Carolina

C O N T E N T S

P R O C E E D I N G S

(8:30 a.m.)

Call to Order

Introduction of Committee

DR. GULUR: Good morning, everybody, and welcome to day 2 of the FDA Pharmacy Compounding Advisory Committee meeting. I would first like to remind everyone present to please silence your cellphones, Blackberrys, and other devices if you have not already done so. I would also like to identify the FDA press contact for the open session meeting, Ms. Lyndsay Meyer. If you are present, please stand.

My name is Padma Gulur, and I am acting chairperson of the Pharmacy Compounding Advisory Committee, otherwise referred to as PCAC. I will now call the committee to order.

We ask those at the table, including FDA staff and committee members, to introduce themselves starting with the FDA representative to my left and moving along to the right side, ending with the industry representative, Dr. Ned

Braunstein.

MS. EURE: Khelin Eure, Office of Regulatory Policy.

DR. BERTHA: Craig Bertha, Office of New Drug Products.

CDR AGARABI: Cyrus Agarabi, Office of Pharmaceutical Quality.

MS. AXELRAD: Jane Axelrad, associate director for policy, CDER and the agency lead on compounding.

DR. ROGERS: Brian Rogers, Office of Process and Facilities.

DR. FLAHIVE: Jim Flahive, CDER, Compliance.

DR. BORMEL: Gail Bormel, CDER, Office of Compliance, Office of Unapproved Drugs and Labeling Compliance.

DR. HONG: Cindy Hong, DFO for Pharmacy Compounding Advisory Committee.

MS. DAVIDSON: Gigi Davidson, chair of the compounding expert committee for USP and USP's representative on this committee.

DR. HOAG: Steve Hoag, from the University

of Maryland.

MR. HUMPHREY: William Humphrey from St. Jude Children's Research Hospital.

DR. DiGIOVANNA: John DiGiovanna, dermatologist with the National Cancer Institute, NIH.

MS. JUNGMAN: Elizabeth Jungman, director of public health programs for The Pew Charitable Trusts.

DR. PHAM: Katherine Pham, NICU pharmacist, Children's National Medical Center.

DR. VAIDA: Allen Vaida from the Institute for Safe Medication Practices.

DR. WALL: Donna Wall, clinical pharmacist, Indiana University Hospital and representing NABP.

MR. MIXON: Bill Mixon, The Compounding Pharmacy, Hickory, North Carolina.

DR. BRAUNSTEIN: Ned Braunstein, Regeneron Pharmaceuticals. I'm the pharmaceutical industry representative.

DR. GULUR: Thank you. We will begin the FDA presentation by Dr. Brian Rogers. He will

speak on metered dose inhalers.

MS. AXELRAD: Actually, sorry, Dr. Agarabi is going to start, and he's going to set the stage here to remind people about the discussion we had at the June meeting. We haven't talked about this since June when we first discussed the difficult to compound list and the statutory provisions, and then the criteria that we were proposing.

So Dr. Agarabi is going to start the discussion and lead you back to what the statute says and what we've done with regard to the criteria since our last discussion, and then we'll go into the presentations.

DR. GULUR: Okay. I will just read some advisory committee topics here.

For topics such as those being discussed today, 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.

Let us begin. We will now have Dr. Cindy Hong read the Conflict of Interest Statement. Thank you.

Conflict of Interest Statement

DR. HONG: 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 Board of Pharmacy, the United States Pharmacopeia, and the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

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

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a

particular individual's services outweighs his or her potential financial conflict of interest when interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services, which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for the 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 session, the committee will discuss two categories of drug products nominated for the list of drug products that present demonstrable difficulties for compounding. These categories of drug products are metered dose

inhalers and dry powder inhalers. The nominators who nominated the category of drugs or specific drug products in the category will be invited to make a short presentation supporting the nomination.

This is a particular matters meeting during which general issues will be discussed. Based on the agenda for today's meeting and all financial interest reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the topic at issue.

We would like to note that Dr. Donna Wall is a representative member from the National Association of Board of Pharmacy and that Ms. Gigi Davidson is a representative member from the United States Pharmacopeia.

Section 102 of the Drug Quality and Security

Act amended the Food, Drug, and Cosmetic Act, with respect to the advisory committee in compounding, includes representatives from the NABP and USP. Their role is to provide the committee with the points of view of the NABP and USP.

Like the other members of the committee, representative members are not appointed to the committee to provide their own individual judgment on the particular matters at issue. Instead, they serve as the voice of NABP and USP, entities with the financial or other stakes in the particular matters before the advisory committee.

With respect to FDA's invited industry representatives, we would like to disclose that Dr. Ned Braunstein and Mr. William Mixon are participating in this meeting as non-voting 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 and temporary voting members that if the 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 regarding the topic at issue that could be affected by the committee's discussions. Thank you.

DR. GULUR: We will start the FDA presentation on introduction of Demonstrably Difficult to Compound and review of criteria by Lieutenant Commander Agarabi.

Presentation - Cyrus Agarabi

CDR AGARABI: Good morning. My name is Cyrus Agarabi, and I am a product quality researcher and reviewer in the Office of Biotechnology Products in the Office of

Pharmaceutical Quality. I'm going to provide a brief introduction to the demonstrably difficult to compound drug products and review of the criteria to provide an update from the discussions we had in previous Pharmacy Compounding Advisory Committee.

Sections 503A and 503B include conditions that must be met for a drug product to be eligible for exemptions from certain FDCA provisions. Both include a condition on difficult to compound products.

Section 503A states that the compounded drug product is not one identified by FDA 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.

Section 503B states that the compounded drug or a category of drugs either is not identified on a list published by the FDA as one that presents demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug or a

category of drugs, taking into account risks and benefits to patients, or is compounded in accordance with conditions that are necessary to prevent the drug or category of drugs from presenting such demonstrable difficulties.

In June of 2015, the proposed evaluation criteria was presented to the Pharmacy Compounding Advisory Committee. Six criteria included: 1) complex formulation; 2) complex drug delivery mechanism; 3) complex dosage form; 4) bioavailability; 5) compounding process complexity; and 6) physicochemical or analytical testing complexity.

The Pharmacy Compounding Advisory Committee provided feedback on the proposed evaluation criteria, and at the June 2015 meeting, the committee recommended consideration of the following inclusion into the criteria.

One is the compatibility and/or stability of the active pharmaceutical ingredients in the final dosage form; second, the container closure system, which may interact with the compounded drug; and

finally, the toxicity of the drug as it relates, 1) potential harm to the patient or caregiver, and 2) potential toxicity due to carry-over or cross-contamination.

Based on the feedback received by the Pharmacy Compounding Advisory Committee, we have updated criteria 1 and 3 to incorporate the committee's recommendations regarding stability and container closure. Those revisions will be presented in subsequent slides.

The handling of hazardous drugs, for example, toxicity, may be addressed elsewhere. For example, cGMPs for outsourcing facilities is pertinent to 503B's. USP Chapter 800, Hazardous Drugs Handling in Healthcare Settings, is appropriate for 503A's. Additionally, in the existing difficult to compound criteria number 5 on compounding process complexity, there is language that addresses specialized facility and/or equipment, which may be pertinent to the handling of hazardous drugs or compounding of hazardous drugs.

We've also revised the document to clarify the description of each factor to more specifically track the statutory language. These changes do not impact how we are interpreting or applying the criteria.

Based on the recommendation to consider stability and compatibility, criterion 1, complex formulation, was revised. The new language can be seen in red. The compatibility and/or stability, physical and chemical, of the API or APIs and/or excipients in the final dosage unit may also be evaluated to determine if the compounded drug product has a complex formulation.

Based on the recommendation to consider container closure, criterion 3, complex dosage form, was revised. The new language can be seen in red. Complex dosage form also refers to container closure systems that may interact with the compounded drug and affect its intended use, either through physical, such as inconsistent dose administration, or chemical interactions between the compounded drug and the container closure

system.

Today, two drug products are being proposed for the difficult to compound list. They are 1) metered dose inhalers, which is being presented by Dr. Brian Rogers, a chemistry manufacturing controls reviewer in the Office of Process and Facilities in the Office of Pharmaceutical Quality; the second is dry powder inhalers, which is presented by Dr. Craig Bertha, a CMC lead in the Office of New Drug Products in the Office of Pharmaceutical Quality.

I'd like to thank the committee for their attention, and we can answer questions regarding the updated criteria at this point. Thank you.

DR. GULUR: We will begin the FDA presentation by Dr. Brian Rogers. He will speak on metered dose inhalers.

FDA Presentation - Brian Rogers

DR. ROGERS: Good morning. I am Brian Rogers from the Division of Process Assessment II in the Office of Process and Facilities. I'm going to present today metered

dose inhalers and why we consider them difficult to compound; the review team who made up these slides, myself and Jianmeng Chen from clinical pharmacology.

As a background, MDIs deliver metered aerosols to lungs. They use the oral inhalation route of administration, and they deliver a small precise formulation volume, usually between 25 and 100 microliters.

The most common uses are the treatment of asthma and chronic obstructive pulmonary disease, COPD. Other uses are for respiratory infections, cystic fibrosis, and sometimes systemic drug delivery.

The formulation in an MDI may be either a suspension or a solution. The formulation components include the API, a propellant, which is the major component by a lot, and the co-solvent in a solution formulation, and usually a surfactant in a suspension formulation.

MDIs are a pressurized system where the propellant is a liquefied gas, and its rapid

expansion provides the energy to create the aerosol out of the orifice. The MDI components are critical in that the container surfaces should be inert to the physically unstable formulation.

The canister is the container, which is sealed by the metering valve to contain pressure. These devices may contain sufficient formulation for hundreds of individual doses. A metering valve needs to consistently measure a precise amount of formulation, and it seals the canister to protect the bulk formulation from the environment.

The actuator creates the aerosol by evaporation through the orifice, and the orifice is critical in that it needs precise dimensional control to create a consistent plume.

Here is a design of a typical MDI. This is the canister, which is the basic container of the formulation, and the MDI device here is shown inverted. Here is the metering valve, and there's a metering chamber in here, which meters the formulation.

This is the actuator, this part here. And

when the MDI is compressed, the formulation is ejected from the metering chamber, out the orifice, into a plume, which is inhaled by the patient. Over here is a design of a typical metering valve where the metering chamber is in this area. This gasket here seals the valve to the canister.

Critical aspects of MDIs are they must deliver consistent dosing to ensure safety and efficacy and also to determine the correct site and quantity of API deposition.

The critical performance attributes are the aerodynamic particle distribution, or APSD, and the delivered dose uniformity, or DDU. The APSD determines the site of deposition, and it has a very narrow effective range of API particle sizes in typically less than 5 microns. The DDU determines how much is deposited in the airway, and it's affected by manufacturing formulation and container closure.

Critical API properties that may affect safety and efficacy include the particle size distribution, particle morphology, polymorphic form

of the drug substance, solubility, bulk density, moisture or residual solvent content impurity.

Excipients include the propellant, which is a poor solvent, any co-solvent, which is necessary in a solution formulation, a surfactant that is necessary to stabilize a suspension. And one of the major issues for excipients is that there's no suitable compendial monographs for inhalation grade materials currently.

Suspension formulations need tight controls to maintain stability. The stability is affected by API properties. The API density can cause creaming or settling in a liquid formulation, which may impact dose uniformity. Adherence of the API to the container closure or other formulation particles is possible.

Ostwald ripening, which is a recrystallization process, may increase the particle size distribution; and changing of the polymorphic form in a suspension is possible, which may create solubility and stability issues.

Extensive characterization studies are

necessary with the proposed devices to detect formulation, physical instability or formulation interactions with the device. It's needed also to optimize the concentration of additives. The instability may result in subtherapeutic or supratherapeutic dosing.

In conclusion, MDIs have a complex formulation that presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on safety and efficacy.

It's critical that it promotes delivery of consistent API mass. They need consistent size droplets or particles from the metering valve under all in-use conditions throughout life. MDIs have unique components. They need predictable and controllable chemical composition and physical stability.

The solid formulation components are physically unstable, and incorrect formulation will not aerosolize correctly and could deliver too much or too little drug affecting the safety or effectiveness of the compounded drug.

MDIs have a complex drug delivery mechanism. It is critical that MDIs consistently measure and deliver a complex formulation to ensure safety and efficacy. Drug delivery determines the drug product performance and is tied to the formulation properties. The actuator used to produce consistent aerosol plume geometry for consistent dose delivery.

The metering valve needs to deliver a consistently fine APSD for appropriate lung deposition. It should be inert to formulation, chemically and physically, and each drug product has unique priming characteristics, which need to be determined.

Canister surfaces should be inert to formulation components, and gaskets and O rings which seal the device should be inert to pressurized organic formulations, should prevent the loss of volatile formulation components, and should prevent contamination by undesirable impurities or environmental components and maintain physical stability.

Formulation aerosolization is complex and difficult. It's the result of an interaction between the formulation and the delivery mechanism. MDIs have drug-specific priming and cleaning requirements where the physical characteristics of the API and the excipients are critical for aerosolization.

Knowledge of optimization is needed on the formulation, the container closure and actuator design in the presence of the formulation and can't be done individually. Manufacturing process, including parameters and controls, need to be optimized, and also the packaging needs to be optimized.

Conclusion. The MDIs have a complex drug delivery mechanism because the delivered dose to the patient is critically dependent on formulation composition, formulation components, characteristics, and container closure surface condition, composition and design. The complex drug delivery mechanism presents a demonstrable difficulty for compounding that is reasonably

likely to lead to an adverse effect on safety or effectiveness of the MDI.

MDIs are complex dosage forms. A sophisticated container closure system is critical to MDIs. The container closure consists of the container or metal canister, a delivery system, which is an actuator and a metering valve. The container closure components have critical tolerances and surface composition. They need to accurately and consistently measure the liquid formulation.

Again, the API may adhere to surfaces, which may affect dose delivery, and improper materials of construction may lead to impurities into the formulation from plastic and elastomeric components.

The formulation and the container closure physical interactions are complex. Valve to canister and valve stem sealing is critical. The canister metering valve seal is held in place by a precisely-crimped ferrule.

The seal should allow valve stems to move

freely and yet prevent pressurized propellant from leaking as a gas and protect the formulation from the environment moisture and oxygen. MDIs should deliver a precise quantity and form of API as an aerosol to the patient's airways.

MDIs have unique formulation properties. The organic liquid phase is normally pressurized at around 97 psi at 25 degree centigrade, the propellant being HFA-134a typically.

They also have high energy solids in suspension. Again, they're typically less than 5 microns in size and have a high surface area. The amorphous physical form is often the required physical form, and it's the least stable of the polymorphic forms.

Dynamic interactions between the container and the formulations determine the APSD and the dose delivered. Both of these are critical attributes for safety and efficacy.

MDIs often need protective secondary packaging such as a foil pouch. This provides additional protection from moisture and oxygen

ingress. It's necessary when performance deterioration is observed on storage, and the need for protective packaging is established by stability studies.

In conclusion, the precise functioning and inert composition of the container closure components, as well as mitigation of the high energy nature of the formulation, are necessary to achieve and maintain a necessary performance of the dosage form. The complexity of the dosage form presents demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the MDI.

Bioavailability of drugs in MDIs is difficult to achieve and assess. For a local-acting MDI, systemic bioavailability is used to extrapolate the systemic safety. To assess local bioavailability of MDI drug products, a weight of evidence approach includes clinical endpoint studies and pharmacokinetic assessments.

This approach would present a demonstrable difficulty to compounding. For a systemic drug

delivery through MDIs, PK studies in humans are essential to assess the systemic bioavailability.

Bioavailability is complex to achieve and determine for the following reasons: the API PSD polymorphic form and other critical physical properties impact absorption. Absorption obstruction decreases the systemic bioavailability.

Currently, in vitro assessment such as APSD and single-actuation content and DDU, alone are not sufficient to accurately predict lung deposition bioavailability and overall clinical effect.

Currently, there is no single easily reproducible reliable method of measurement that can quantitate the dose delivered by the dosage form and received by the patient, which would be necessary to enable a compounder to consistently make products with delivered dose uniformity falling within acceptable ranges.

In conclusion, for locally-acting drugs applied to the lungs at low doses, measuring local bioavailability does not currently have a single easily reproducible method of quantitation. For a

systemic drug delivery through MDI drug products, systemic bioavailability is not predictable based on in vitro assessment alone. Therefore, achieving and assessing bioavailability of MDIs presents demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on safety or effectiveness of the MDIs.

API and excipient processing is critical to the performance of MDIs. It is critical that APIs and excipients for suspension formulations be micronized in specialized equipment followed by conditioning to assure uniformity of the physical form. API for solution formulations pose a different problem through degradation and absorption of the formulation components by the valve components.

Overall unit-to-unit and batch-to-batch uniformities are dependent on the variability of the formulation filled into the canisters. Formulation filled is dependent on the uniformity of the bulk formulation of the filling system, the blend uniformity of the solids, and the rate of

addition of make-up propellant.

Filling can be accomplished with the formulation cold or under pressure. Both process types have complex requirements for uniform filling, and it's critical to control moisture and that's challenging.

Both cold and pressure filling use equipment specialized for MDI manufacturing such as the homogenizer, a sealed formulation tank, and filling tank. A formulation circulation system is necessary to maintain suspension uniformity. Rotary or stationary filling units with purge, crimping, and filling heads are also necessary.

Manufacturing equipment is difficult to set up and validate because of the large number of process parameters involved. Specialized equipment is also necessary to assure uniformity in both the particle size and concentration, which affect safety and efficacy.

Formulation compounding is critical for MDI performance. Changes in the polymorphic form and PSD during liquid formulation blending and filling

are possible when the API has solubility in an intermediate formulation or blending is not accomplished at sufficiently low temperatures.

Measurement of the bulk formulation properties during filling is difficult since the sealed and pressurized system is used for both filling types. A sealed and pressurized system is crucial to preventing ingress of moisture or oxygen or loss of volatile propellant or co-solvent.

Ingress of moisture or oxygen, or loss of the volatile components, should be minimized to prevent the changes in the API particle size distribution. Increased propensity of the API to interact with the container closure components also occurs with the presence of moisture. Changes in the extent of these interactions may cause significant batch-to-batch variability and have a deleterious effect on safety and efficacy.

Formulation filling into the MDI is a critical and complex procedure, which includes either evacuation or purging of the container closure with propellant to eliminate atmospheric

moisture and oxygen.

Sealing of the valve to the canister by precise crimping is necessary, and then filling of the formulation into the canister is also critical. Filling parameters to assure batch-to-batch uniformity include propellant purge weight, crimping dimensions, fill volume, and API content uniformity in the formulation, a total can assay and pressure testing when co-solvents or propellant mixtures are used.

In conclusion, any errors in filling or formulation compounding are reasonably likely to result in delivered dose variability in either the quantity of the emitted drug or its APSD. Insufficient drug delivered to the appropriate part of the lungs as measured by these two parameters will pose an efficacy concern and potentially a safety concern, particularly for rescue medications. Compounding in MDI involves a complex compounding process that presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on safety and

effectiveness of the MDI.

MDIs require complex physicochemical or analytical testing. They need extensive characterization in the development studies to test the formulation, the container closure, and its compatibility with the formulation and the manufacturing process.

Development of specifications and in-process controls for the following is critical since these ultimately determine performance characteristics. They are the raw materials, the container closure components, and manufacturing consistency.

Appropriate API specifications, release, and stability, and retest, and are needed before and after additional processing micronization and conditioning. Controls are needed to maintain consistent API physicochemical properties such as the polymorphic form, the particle size distribution, the surface morphology, water content, and others.

This helps to ensure consistent dosage form performance, including the physical stability, the

drug content for actuation, the aerosol APSD, and these attributes help to assure consistent bioavailability.

Low drug load in suspension, typically 0.1 to 5 microliters per milliliter, is common, and this could lead to a non-uniform drug product. The formulation is difficult to sample in the pressurized system, and unit testing after filling is necessary to ensure accurate and consistent dose delivery.

Typical testing includes assay valve crimp measurements, component fill weight function, and integrity testing. And low drug loading makes periodic in-process testing necessary to assure property suspension uniformity for unit filling.

For lot release testing, APSD is the most critical performance attribute. Testing requires a cascade impactor and analysis of the dose delivered. Complex procedures with low masses of API analyzed may be in an excipient matrix, and difficult to use and qualify compared with other analytical methods.

Leachables testing is critical for safety. One needs to test for impurities from container closure components, and this is complicated by leaching over time by the liquid organic formulation.

Leachables testing uses sensitive specialized analytical techniques at the ppm and ppb levels, and they should be able to quantitate a wide range of chemical structures, and usually, multiple testing methods are needed.

Delivered dose uniformities is another critical performance attribute, and its testing requires special apparatus and support equipment.

Stability testing. The quality and performance of testing covers appropriate storage conditions and performance testing at the beginning and end of product life. In-use period testing includes characterization studies, which are, again, product-specific.

Determination of the in-use period is necessary, which is after exposure of the MDI device to the atmosphere out of the protective

packaging until the labeled number of actuations have been consumed by the patient.

The resting time and priming requirements are also necessary to determine cleaning requirements and temperature and humidity cycling for the purposes of shipping qualification.

In conclusion, MDIs require a complex physicochemical analytical testing because the formulation properties and critical performance parameters of the product require complex analytical devices and procedures. Furthermore, impurities must be quantitated through various sensitive analytical techniques developed specifically for these impurities.

In-process testing of MDIs and control of their manufacturing process using methods unique to MDI manufacturing procedures are critical to minimize unit-to-unit and batch-to-batch variability and to ensure accurate performance throughout the product shelf life and in-use life.

The physicochemical or analytical testing needed for MDIs is so complex that it is likely

that a product quality defect would not be detected, which would lead to an adverse effect on the safety or effectiveness of the compounded drug. Accordingly, the complex testing required for MDIs presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on safety or effectiveness of the MDI.

Our proposal is that, based on the analysis of the evaluation criteria to assess MDIs present demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product and that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the category of drugs.

Taking into account the risks and benefits to patients, we propose that MDIs be included on the list of difficult to compound drug products under Sections 503A and 503B of the FD&C Act. Thank you.

Clarifying Questions from the Committee

DR. GULUR: Clarifying questions for the

presenter? Dr. DiGiovanna?

DR. DiGIOVANNA: Yes. John DiGiovanna. I have a question about the scope of the devices that are included in this. For example, are there similar devices for oral and nasal mucosal administration of drugs, and does this metered dose inhaler encompass devices that may be non-pressurized, for example, squeeze-bottle delivery systems?

DR. ROGERS: No, this particular presentation only covers MDIs that are pressurized.

DR. DiGIOVANNA: So will the regulations exclude those devices that are non-pressurized?

DR. ROGERS: They would be taken up in another proposal at some other time if they're deemed so.

DR. DiGIOVANNA: So they're distinct.

MS. AXELRAD: Yes, they're distinct. And I think that we would have to define the category well enough in terms of metered dose inhalers containing pressurized gas, for example, if that's the recommendation, so that people can understand

what they can and can't do.

DR. GULUR: Dr. Vaida?

DR. VAIDA: Going back to the opening presentation, just so I have it straight in my mind, these compounds would be excluded for 503A. But for 503B, if they showed that they could produce them, they would be okay?

Is that how I read this? I think that's how it was explained.

MS. AXELRAD: We would recommend that we put these on the difficult to compound list for both 503A and 503B. We think that this particular dosage form is so complicated that the only person that could actually do it well is a manufacturer who could do the drug development work. It would be submitted to FDA in an NDA or an ANDA and be reviewed by us, because even an outsourcing facility, if they were doing it, wouldn't have done the drug development work, wouldn't have submitted it to us; we would not have seen it.

So even though they might be making a dosage form under good manufacturing practices, in order

to do that, you have to have information about how you need to do it and the specifications, and the testing, and all of that done before you get to GMPs.

DR. VAIDA: So in essence, this would really be excluded from --

MS. AXELRAD: Yes, this would be on both lists.

DR. GULUR: Dr. Hoag?

DR. HOAG: I'm just wondering, I've never heard of a compounding pharmacist doing this. How many prescriptions per year are in this category?

MS. AXELRAD: As I said last time, we don't know of anybody doing it either. In part, our thinking on this -- and it was the same as we did when we were implementing the law, the '97 law, because this provision was in there originally.

It's to start with something that is relatively easy and not terribly controversial because people are not doing it, so that you can see how the criteria that we've been working on would be applied in a specific instance before we

get to some of the more difficult-to-compound categories, where it will be harder to define them, develop the nuances, and answer a lot of the questions that were raised in the discussions last time.

MS. BORMEL: I would just add that these were nominated for the list, the DTC list.

MS. AXELRAD: It was a nominated -- it was nominated. Of the 71 things, a number of them were metered dose inhalers, but that doesn't mean that people were compounding them. It just meant that somebody didn't want to have them compounded.

MS. BORMEL: Correct.

DR. GULUR: Any other questions?

(No response.)

DR. GULUR: We are scheduled to have a morning break, but we've chosen to work through that break if everyone's in agreement. We will continue with the FDA presentation by Dr. Craig Bertha. He will speak on dry powder inhalers.

FDA Presentation - Craig Bertha

DR. BERTHA: Good morning. I'm

Craig Bertha. I'm the CMC lead in the Office of New Drug Products, and I'm also the liaison for the Division of Pulmonary Allergy and Rheumatology Products, the clinical division. Dr. Chen and I worked on putting together this presentation that I'm going to show today.

In the beginning, I'm going to give a little background information on DPIs. This is a little bit different from the MDIs because there's really no single type of DPI. There's a range of different types. And then, I'm going to go through the various criteria that we examined to put together our proposal and our perspective that these are difficult to compound. And then I'll conclude.

Dry powder inhaler deliver powder formulations topically to the tissue surfaces of the lungs. Most of these are designed for a local effect in the lungs. Systemic drug absorption into the bloodstream from the lung is generally undesirable, although with most of these, there will be some larger particles of drugs that get

into the GI tract, and then there may be some bioavailability from that and related side effects. But generally, they're for topical application to the lungs.

The most common uses are the same as for MDIs, treatment of chronic obstructive pulmonary disease and asthma. And we've also seen applications for treatment of cystic fibrosis, lung infections, and we've approved two dry powder inhalers for the systemic delivery of insulin for diabetic patients, although one of these is not marketed.

DPIs consist of formulated drugs and an associated specific device for delivery by oral inhalation. There are main subtypes. There are the pre-metered type, where the drug is metered into the unit doses at the factory before the patient gets the device; and there are the device-metered DPIs, where the formulation is put into a reservoir, and then as the patient uses the DPI, the device meters the drug. And these proprietary designs, which are patented, vary

widely from the relatively simple type of DPI to very complicated devices.

The drug substances, as for the MDIs, are micronized to very small particle size, typically less than about 5 microns. The doses of drugs are very low, so the formulations generally require the use of carrier excipients as a bulking agent to provide acceptable blend uniformity and dosing uniformity for the final product.

The energy for delivery and deagglomeration, or the release of the drug from the carrier, typically comes from the patient's inhalation maneuver. Formulations often have reduced stability relative to those of more common drug products because of the high energy state of the finely micronized drug.

Formulation, production, and associated control strategies are unique for DPIs, and if these are inadequate, it can result in inconsistent performance and non-optimum dosing of patients.

This diagram here, this figure sort of depicts the operating principle behind most of the

DPIs that the agency has seen. On the left side, you'll see the large, light-colored, rectangular boxed particles of carrier coated with the small micronized excipient particles.

These are either loaded into the reservoir for devices such as the Turbuhaler, or in pre-metered DPI devices such as Diskhaler, Diskus, or HandiHaler. The Diskhaler and the Diskus use blisters for the unit doses, and the HandiHaler uses a gelatin capsule, I believe, for the unit doses.

When the patient inhales from the device, that draws the formulation out of the device. And the energy from the inhalation breaks off, hopefully, a large amount of the API consistently from the carrier, and then these are of a size that can be inhaled into the lungs.

DPIs, generally, they deliver metered aerosol to the lungs by oral inhalation, and they generally deliver small precise amounts. So we can have drugs as small as a few micrograms of drug, all the way up to maybe a milligram of drug at most

per actuation or per inhalation. The dosing needs to be consistent both in terms of the dose and the particle sizes of drugs, which is critical for safety. It also helps ensure that the drug reaches the correct deposition site in the lungs.

The two main critical quality control performance test attributes that we look at, and that are used to test and control dry powder inhalers, are the same as they for metered dose inhalers: delivered dose uniformity and aerodynamic particle size distribution.

The DDU measures the dose-to-dose quantity of the drug emitted for deposition in the airways of patients and expected dosing variability under ideal laboratory circumstances. These are conditions that are done systematically under a very precise airflow conditions. The delivered dose uniformity is affected by manufacturing formulation and DPI device characteristics.

The aerodynamic particle size distribution testing measures the quantity of drug with ranges of known aerodynamic particles sizes. The results

of this testing relate to the actual site of deposition in the airways. However, the relationship of these data can rarely be established with any confidence.

The aerodynamic particle size distribution testing helps assure the necessary range of the API particle size and also the formulation consistency. This parameter can also be affected by the manufacturing of the formulation, the formulation itself, and the DPI device.

Moving from background information, DPIs have complex formulations. The drug and the excipient interactions depend on both the choice of the excipients and controls for API excipient physicochemical properties.

The API excipient interactions help assure that there are sufficient physicochemical stability or adhesion to the formulation, but with substantial consistent deagglomeration being able to occur so that the API can break free from the carrier and be delivered, and that assures reproducible dose performance.

The API excipient interactions are also important because you need to have adequate formulation manufacturer ability for the formulation. It needs to be flowable, and it also has to reduce the amounts of fines that are either lost to the filling equipment or lost to the device.

Formulation robustness is also important because there's high variability with patient-driven dose delivering from patient to patient, so the formulations have to take that into account. Carrier excipients are also necessary with low drug loads to achieve acceptable blend in dose uniformity.

Characterization and control of formulation component properties are critical to yield DPIs with consistent dosing performance and stability, helping to assure safety and efficacy for patients. For the API properties, there needs to be consistent particle size distribution, which is necessary for the drug to reach the site of action.

The fine drug has high surface area or

energy and often requires unique treatment handling and formulation process. The solid state or the crystalline form of the drug determines the kinetic solubility and the bioavailability at the site of action. Special conditioning is often needed to reduce the percentage of amorphous API that results from micronization, which increases the physicochemical stability the API.

As far as the excipients are concerned, there are a few API carrier excipients that have been qualified toxicologically for oral inhalation impurities critical for safety. Excipients such as lactose need to be compatible with the API to assure chemical stability.

Carrier surface stabilizers are often necessary to dampen high energy interactions with carrier and fine API and achieve the needed balance of API carrier interparticulate interactions, the sealed formulations that produce higher and consistent amounts of fine particles upon delivery from the device, and this also would help increase the shelf life of the product so that there would

be no changes in the particle size with time.

High level of purity of APIs and excipients necessary for oral inhalation route of administration is usually not addressed by the current compendial API excipient monographs, but hopefully that will get better with time. Patients with diseased lungs are often more sensitive to formulation impurities.

Formulation stability. Unusually consistent and stable formulations are critical to DPIs to prevent dosing variability. Formulation stability can be affected by the API and excipient properties. You can have recrystallization of amorphous material from the micronization, and this can lead to particle bridging and change in the APSD. There can be changes in the drug's polymorphic or crystalline form. They can alter the drug kinetic solubility, and that can lead to altered lung bioavailability.

Extensive formulation development characterization studies are necessary to determine the need for stability additives or component

conditioning to also help assure formulation stability with optimized drug load and increase the ability to achieve blend uniformity.

In conclusion, DPIs have complex formulations that require extensive development, characterization, and controls to assure acceptable dosing performance. The complex formulations present a demonstrable difficulty for compounding that is reasonably likely to lead to adverse effect on the safety or effectiveness of the DPI.

DPIs have complex drug delivery mechanisms. Unlikely most drug products, dosing of drug from DPIs normally depends on the patient inhalation maneuver, so patients really are a part of the drug delivery mechanism. The patient inhalation withdraws the drug formulation from the delivery device. The patient inhalation deagglomerates or breaks up the formulation to yield the inhalable sized API particles.

Patient inhalation parameters such as their airflow rise or the peak flow that they can achieve can vary widely from patient to patient or day to

day from a single patient. So DPI designs, both with the device, with the formulation, need to be optimized to be robust to varying patient inhalation parameters and not contribute to dosing performance variability.

An ideal DPI device would be intuitive to use, robust, with consideration given to the variable patient inhalation parameters, rugged to manipulation, use, or unintentional misuse, and at expected storage and shipping conditions, be informative of the remaining number of doses and have limited hold-up of the high energy drug so that cleaning requirements aren't too onerous.

Since drug delivery depends on patient usage conditions, which is inherently variable, extensive data are critical to characterize the drug product and create patient-oriented labeling; so instructions for use for the patient and the storage conditions to limit drug delivery variability with patient use as much as possible.

The characterization studies usually include an examination of the stability of the formulation

after removal of protective packaging; the behavior of the DPI after undesirable storage or environmental exposure; the actual impact of patient use on the remaining doses on the DPI; any effect of orientation during use either with loading of the dose or with the delivery of the dose during patient use; drug loss to the device and any necessary cleaning that that would lead to; and drug available near exhaustion, so devices that don't have lockout and have reservoirs -- the device metered DPIs -- we like the characterization of how the dose drops off at the end; the effect of varying flow rate on dosing performance considering typical patient-generated flow rates that need to be determined, and this is dependent on the resistance of the device; and also device ruggedness testing.

In conclusion, DPIs have complex drug delivery mechanisms, so they must be designed with formulations and associated devices that in combination provide consistent drug delivery both in dosing and the aerodynamic particle size

distribution to patients with widely varying inhalation characteristics.

DPIs have a complex drug delivery mechanism that present a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect in the safety or effectiveness of the DPI.

DPIs are a complex dosage form, so regardless of the underlying complexity of their devices, DPIs have complex formulations, have complex drug delivery mechanisms, and must be designed to perform reproducibly with the variation inherent in patient inhalation-driven dosing.

In conclusion, DPIs are complex dosage forms that present a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the DPI.

Bioavailability of drugs in DPIs is difficult to achieve and assess. For locally-acting DPIs, systemic bioavailability is used to extrapolate to systemic safety. To assess

local bioavailability of DPI drug products, a weight of evidence approach typically includes clinical endpoint studies and pharmacokinetic assessments in patients. This approach would present a demonstrable difficulty to compounding. For systemic drug delivered through DPIs, pharmacokinetic study in humans is essential to assess the systemic bioavailability.

Bioavailability is complex to determine. The drug particle size distribution, its crystalline polymorphic form, and other critical physical properties for the formulation likely impact absorption.

Absorption obstruction decreases systemic bioavailability. Currently, there are no in vitro assessments such as aerodynamic particle size distribution or determination of dose content alone. These are not sufficient to accurately predict lung deposition or bioavailability and overall clinical effect.

Currently, there is no single easily reproducible reliable method of measurement that

can quantitate the dose delivered by the dosage form and received by the patient, which would be necessary to enable a compounder to consistently make product with delivered dose uniformly falling within acceptable ranges.

In conclusion, for locally-acting drugs applied to the lung at low doses, measuring local bioavailability does not currently have a single easily reproducible method of quantitation. For systemic drug delivery through DPI drug products, the systemic bioavailability is not predictable based on in vitro assessment alone.

Therefore, achieving and assessing bioavailability of DPIs presents demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on safety or effectiveness of DPIs.

DPIs require complex compounding processes. DPIs necessitate API with small particle size for inhalation, and typically the APIs are micronized with specialized equipment. Further conditioning may be needed to control the physical properties of

micronized API to achieve the desired performance reproducibility and formulation stability.

Typical low drug loading needs extra care during processing to achieve adequate blend uniformity. There can be specialized seal integrity in-process testing necessary to help assure functionality of any protective packaging.

Optimizing formulation characteristics for device filling and drug product usage may require additional processing manufacturing considerations. There can be formulation stabilizers used such as lubricants or fine carrier particles to achieve the necessary balance between the API and the excipient interactions to achieve dosing performance and stability.

There needs to be control of excipient physicochemical properties and particle size, and applicants may need to determine the need for additional environmental controls during manufacturing and/or if they need to apply DPI protective packaging such as desiccants, oxygen scavengers, and foil-overwrap.

In conclusion, manufacturing a DPI requires substantial development to understand the optimal formulation manufacturing and device characteristics necessary to provide a robust drug product that can provide the accurate and precise dosing of patients with widely varying inhalation characteristics.

Any errors in formulation in compounding and device filling are reasonably likely to result in delivered dose variability in either the quantity of the emitted drug or its APSD. Such scenarios could result in insufficient or excessive drug delivered to the appropriate parts of the lungs, potentially leading to a lack of efficacy or other patient safety concerns.

Compounding a DPI involves a complex compounding process that presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the DPI.

DPIs require complex physicochemical or analytical testing. In addition to routine tests

applied to most drug products, some critical DPI quality control testing is unique, complex, and specialized.

Drug product component testing for DPIs is a critical part of the overall quality control strategy to ensure DPI dosing performance and low variability; that is sufficient physical stability of the formulation, on-target drug content and formulation per actuation in terms of the assay and the delivered dose uniformity, and the desired aerodynamic particle size distribution for the delivered drug.

API excipient component testing includes crystalline form or amorphous content, the particle size distribution, particle surface, texture measurements, surface area, and moisture content.

For the device and packages, there can be dimensional measurement requirements for certain critical components. For example, for device metered DPIs, the components that meter out the drug, the small quantities of formulation need to have concise dimensional tolerances.

There can be testing to assure consistency of composition of the surface characteristics of components in the flow path of the exiting drug formulation because this can lead to variability and the hold-up of the drug as it exits the device.

There can be functional testing, for example, for a dose counter function, and this is crucial for devices that are for rescue of asthma attacks. There can be moisture or vapor transmission rate testing to gauge protective capability of foil pouch or other protective packaging.

DPI lot release and stability testing for key performance related parameters include those for the aerodynamic particle size, which is a critical quality control test attribute for these drug products, and that requires cascade impactor analysis of dose delivered. This is using specialized equipment and analysts have to be trained. This is a complex procedure. Low masses of API are captured and analyzed, so the methods need to be sensitive.

DPIs present a particular challenge here due to particle bounce and re-entrainment, so the cascade impactor has to be treated to control for that. The test is difficult to perform and validate compared to other analytical methods, and the cascade impactor equipment require specialized handling and maintenance.

Delivered dose uniformity testing is also a critical quality control to test the attributes of DPI and requires specialized equipment and analyst training.

Both of these tests and other tests for other parameters are performed for the dry powder inhalers during the stability studies to determine the appropriate storage conditions set, the drug product expiration dating period, and qualify any protective packaging that may have been used.

Getting back to the production of the instructions for use for patients and the storage conditions, there has to be extensive drug product characterization laboratory testing to create those labels. There are studies to determine the

appropriate in-use period after the protective packaging is removed. There can be temperature cycling studies to look at extreme environmental or storage conditions that may be encountered during the shelf life of the product.

There can be returned samples from the clinical trials, partially used returned samples that are tested in the laboratory to determine if there's any effect of the patient use on the remaining doses.

There can be tests designed in the laboratory to look at orientation effects in terms of the dosing performance. There are studies to look at drug hold-up and any necessary cleaning requirements that need to be included in the labeling.

As I mentioned before, for device metered DPIs that don't have a lockout at the end, there needs to be studies to characterize the drug available near exhaustion or when the counter reads zero if the patient happens to use it beyond that point. Then there are tests to examine the varying

flow rate and how that affects the dosing performance as well as ruggedness tests.

In conclusion, the quality control testing of component materials, both prior to and during the manufacture, and the final testing of the finished DPI drug product for lot release and stability characterization has a complex methodology to help assure the critical quality attributes related to dosing and performance are attained.

These tests are difficult to develop, validate, and perform routinely. They use highly specialized and unique equipment and analysts that have received considerable training. Accordingly, the complex testing for DPIs presents a demonstrable difficulty for compounding that is reasonably likely to lead to an adverse effect on the safety or effectiveness of the DPI.

Based on the analysis of the evaluation criteria, to assess if DPIs present demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or

effectiveness of the drug product and that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the category of drugs, taking into account the risks and benefits to patients, the agency proposes that DPIs be included on the list of difficult to compound drug products under Sections 503A and 503B of the Food, Drug, and Cosmetic Act. Thank you.

Clarifying Questions from the Committee

DR. GULUR: Clarifying questions? Dr. DiGiovanna?

DR. DiGIOVANNA: Yes. John DiGiovanna. The issue I have with this is I don't have a clear understanding of how the MDI and DPI, of the scope of them. We've had very clear presentations about how complex they can be. I don't understand the other pole of how simple they can be.

I'm not quite sure I understand the difference between the definition of this and my having a cold and going to a drug store and buying a squeeze bottle of Afrin nose drops or a bottle of saline in a drop with a squeeze bottle. I'm not

certain I understand that that would not be included in this.

The other thing I don't fully understand is these are the most clearly complex situations. What is the other pole of that? Are there other products that are very simple, that are not pressurized, that would be easy to manufacture, that would be included in this because of the definition?

DR. ROGERS: In the case of MDIs, there are no way to -- there's no way to get a drug into the lungs using a squeeze bottle or a simple device. The only way to get a pressurized aerosol into the lungs is with the devices I've shown.

There is no other way to create an aerosol that is, the formulations I described, other than an MDI. Nasal sprays and the kind of squeeze bottles you described are very different in their performance characteristics. There's no overlap in those dosage forms between those and the MDIs.

DR. DiGIOVANNA: So nasal inhalers, metered, are not covered under this in any way.

DR. ROGERS: No.

DR. DiGIOVANNA: So there's a distinction somewhere between intraoral mucosal administration and intranasal administration in these products? Because it's not clear to me but --

DR. ROGERS: Yes, the nasal sprays are intended to be deposited basically where they're administered. The aerosols from an MDI have to get past the throat and tongue where there is some deposition evidently, but the majority of the dose is targeted to get way into the lungs, like fine smoke particles. It's a very different set of performance parameters.

DR. DiGIOVANNA: I clearly agree with you. I just don't understand how the way this is written separates out the nasal inhalers from the MDIs.

DR. GULUR: Dr. Agarabi?

CDR AGARABI: To address your question directly, we do define what the MDI consists of, one or more APIs dissolved or suspended in propellant. We have a liquefied gas under pressure. What you're talking about, I go to the

drug store and I get a pump spray, would not fall under that definition because it's not under pressure.

To your other point, there are more simple compounding options for the inhalation route that we are not discussing today. We are not discussing products that might be nebulized. We are focusing only on the types of MDI and DPI sort of complicated dosage forms that you mentioned earlier on.

DR. DiGIOVANNA: Thank you.

DR. BERTHA: I think we're also using these definitions, metered dose inhaler and dry powder inhaler, as we've defined in our agency guidance, where we equate a metered dose inhaler with an inhalation aerosol meant to deposit drug in the lungs. That guidance also talks about nasal aerosols, which would be a lot like an MDI but for depositing drug in the nose. This specifically covers metered dose inhalers, which are the equivalent of an inhalation aerosol, so it's for lung delivery.

As far as the dry powder inhalers, it's also the same thing, that in our agency guidance, we equate them with inhalation powders. That name is consistent, and it only means when the drug is to go to the lungs, not for a nasal deposition.

In the context of the guidance and the use of these names, I think it's pretty clear that it's only for the drugs for deposition into the lungs, not nasal.

DR. GULUR: Dr. Vaida?

DR. VAIDA: You had mentioned in the beginning, too, that the device designs are proprietary and usually patented. Maybe it holds true with the MDIs, too, but even you were able to compound something, you would also have to, more than likely, come up with your own device design.

DR. BERTHA: I know of one device which had its patent run out, and there are a lot of sponsors that are buying that device from a manufacturer that's manufacturing it.

So there is at least one that's out there that you can get. But still, you would have to get

over all those other hurdles I mentioned. You'd have to have development work. You'd have to come up with a formulation that was robust so that it would deliver the same amount all the time, and it would still not get you away from the fact that if you produced a drug that in the laboratory delivered the right amount of drug, or what you thought was the right amount of drug, with the right amount of particle size, you still wouldn't have any connection to what that meant to the patient without the bioavailability aspect of it.

Even if you were able to get that simple device and compound something, you still wouldn't be able to know if it would work or not, or if it would be safe or not.

DR. GULUR: If there are no further questions -- Dr. Hoag?

DR. HOAG: Quick question. Like for example, the Spinhaler and the HandiHaler, what if some physician said, oh, I want half the dose in there, where they would open up the capsule and pour a little out or something? Is that covered

under this?

MS. AXELRAD: I think what we're saying is, in some cases, it's so inherently difficult to compound, that it just shouldn't be done, because let's say a doctor decided that somebody should get half of whatever amount coming out into your lungs than would come out through the metered device that they get, they wouldn't be capable -- we don't think a compounder would be capable of putting together a drug and a formulation that would actually do that.

That's the nature of this, that these things are so inherently difficult to do. We went through a fairly extensive presentations because, frankly, I don't think people realize it. They might think, oh, I can just buy this device. Other companies are buying it, and I'll put something in it. And a doctor might think it's really a good idea, and they would write for it, and a compounder would make it.

We're basically saying these are a lot more complex that most people perhaps realize, and

that's why we're proposing that they be put on the list.

DR. HOAG: I was just kind of wondering if compounding included modification of this, and it sounds like it does.

DR. ROGERS: In a technical way, the example that you described where you would take a capsule and remove part of the dose in order to half the dose, for example, for one thing, just exposing the drug to the atmosphere like that potentially really cripples the dose delivery.

Taking half of the formulation and putting it back in the capsule would most likely cause a significant drop in the dose delivery to the lungs. Also, the formulation as contained in the capsule is what is analyzed as being delivered through the device. So what would happen potentially is that removing half of the formulation would actually be removing either much more or much less than half of the active drug.

There is no way to determine the position in the capsule of the majority of the drug. It may be

uniformly dispersed throughout the formulation and it may not be because all we really measure is what comes out.

So you're rolling dice by doing anything to any kind of capsules or container closures that is outside of the labeling of a labeled drug, approved drug.

DR. HOAG: Maybe a comment, too. I'm just thinking, like you're talking about delivery to the lungs and things and thinking forward, there are things like chromaline that are delivered by nebulizers and all those types of things, which are a little bit outside of that. But microbial stability I think could be a factor that's very important in some of these things.

DR. GULUR: Any further questions?

(No response.)

Committee Discussion and Vote

DR. GULUR: There are no nominator presentations for this, and the FDA did not receive any registrants for the open public hearing session, so we will move on to committee discussion

and voting.

We will now begin the panel discussion portion of the meeting. We will start with metered dose inhalers. Any questions?

(No response.)

DR. GULUR: Dry powder inhalers? Dr. Davidson?

MS. DAVIDSON: The dry powder inhalers, I think he makes a good point, that it should be very clear that compounded capsules cannot be prepared to go in these DPI devices because they're commonly compounded in lactose powder, and I could see maybe someone making that connection.

MS. AXELRAD: These are the kinds of things we would like to hear from you. And when we're doing the rulemaking and we're dealing with making sure that we're clearly defining the categories and explaining our reasoning, things like that are very helpful to know, what is it, how is the best way to differentiate these from other things, and what are things that one would be concerned about if somebody was doing something that might fall under

the activity of preparing or compounding a dry powder inhaler.

DR. GULUR: Dr. DiGiovanna?

DR. DiGIOVANNA: Again, I appreciate the definition, but sometimes the devil is in the details. I still think of going to the drug store and looking at the directions on the bottle that says to insert into the nostril, squeeze -- which to me can be contrived as a metered dose -- while inhaling, which can be contrived as a metered dose inhaler.

I think my vote will be contingent on this being defined as a pressurized apparatus to target the lungs, which I think you have portrayed that to be.

DR. GULUR: If there's no further discussion, we will end the discussion and start the vote.

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 voted will be complete.

Voting will be on the two drug products just presented. All vote questions related to whether these products should be included on the demonstrably difficult to compound list. After the completion of each vote, we will read the vote from the screen into the record and then hear individual comments from each member.

We will repeat the first question. So vote yes, no, or abstain for this question. FDA is proposing that metered dose inhalers be placed on the list of drug products that present demonstrable difficulties for compounding in accordance with Sections 503A and 503B of the FD&C Act.

Should metered dose inhalers be placed on the list? Before you answer, if you vote yes, you are recommending placing these drug products on the difficult to compound list under Sections 503A and 503B of the FD&C Act. If a drug product is included on the list, it cannot be compounded in accordance with Sections 503A and 503B.

To repeat that question one more time, should metered dose inhalers be placed on the list? If you could vote now.

(Vote taken.)

DR. HONG: Question 1 for MDIs, we have 9 yeses, zero noes, and zero abstain.

DR. GULUR: We will start with the member comments. We'll start with Ms. Davidson at Dr. Wall's request.

(Laughter.)

MS. DAVIDSON: I voted yes due to the conclusions made in both FDA speaker presentations.

DR. HOAG: Steve Hoag. I voted yes. I thought the FDA did a very good job of presenting the reasons as to why this should be on the list. Also, some of the comments about clarification, I think are important to take in account.

MR. HUMPHREY: William Humphrey. I voted yes. I agree with the FDA's presentation and assessment.

DR. DiGIOVANNA: John DiGiovanna. I voted yes. I agree with the very elegant presentation of

the FDA. Again, however, I believe that what they've described are pressurized complicated devices intended to target the lungs, and I think the regulations must include that if there are similar devices which have other targets, such as the nasal mucosa, that they do not fall under this category.

MS. JUNGMAN: Elizabeth Jungman. I voted yes because I felt it met all the criteria as FDA described.

DR. PHAM: Katherine Pham. I voted yes because I also agreed with the FDA's assessment and do also support that, really, only the drug manufacturers probably have the capacity to take on products like these.

DR. VAIDA: Allen Vaida. I voted yes, going along with the conclusions of the FDA.

DR. WALL: Donna Wall. I voted yes because of the presentations and the conversations surrounding it.

DR. GULUR: Padma Gulur. I voted yes as it was clearly demonstrated that this would be

difficult to compound.

For our second question today, the FDA is proposing that dry powder inhalers be placed on the difficult to compound list. Should dry powder inhalers be placed on the list?

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

To repeat the question, should dry powder inhalers be placed on the list? Please vote now.

(Vote taken.)

DR. HONG: Question 2 for DPIs, we have 9 yeses, zero noes, zero abstains.

DR. GULUR: We will begin with member comments. Ms. Davidson?

MS. DAVIDSON: Gigi Davidson. I voted yes because of the FDA presented conclusions with the caveat that it be made very clear that dosage forms to be delivered by dry powder inhalers are also not

to be compounded.

DR. HOAG: Steve Hoag. I voted yes for all the reasons stated, and I agree with everything said.

MR. HUMPHREY: William Humphrey. I voted yes. I agree with the FDA's assessment.

DR. DiGIOVANNA: John DiGiovanna. I voted yes. I agree with the FDA's assessment with an indication that the presentation was for lung delivery.

MS. JUNGMAN: Elizabeth Jungman. I voted yes because I felt like it met the criteria per the FDA's presentation.

DR. PHAM: Katherine Pham. I voted yes also because I agree with the FDA's assessment.

DR. VAIDA: Allen Vaida. I voted yes, going along with the FDA's presentation.

DR. WALL: Donna Wall. I voted yes for all the reasons previously stated.

DR. GULUR: Padma Gulur. I voted yes for reasons previously stated, and then again endorse Ms. Davidson's point on the formulations.

With that we are closing for the day. We await any last words from the FDA officials.

MS. AXELRAD: Again, I thank you very much for your thoughtful consideration of the issues that we brought to you. I'm looking forward to continuing to deal with the difficult issues.

I think that we're going to get to some more difficult issues as we go through the categories, particularly of difficult to compound drugs. We'll be bringing in future meetings some of the additional categories of the 71 categories that were nominated and also specific drugs, as well as some categories that we ourselves have been considering. We'll see how well the criteria hold up when we do those.

But thank you for your work yesterday and today. We appreciate it.

Adjournment

DR. GULUR: Thank you. The meeting is adjourned.

(Whereupon, at 10:02 a.m., the meeting was adjourned.)