FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACY COMPOUNDING ADVISORY COMMITTEE

(PCAC)

Tuesday, March 8, 2016

Morning Session

8:30 a.m. to 12:20 p.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

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Staff Clinician, DNA Repair Section
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Donna Wall, PharmD

National Association of Boards of Pharmacy (NABP) Representative

Clinical Pharmacist

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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

TEMPORARY MEMBERS (Voting)

Lenore Buckley, MD, MPH

(Participation in quinacrine, boswellia, D-ribose, and chondroitin discussions)

Professor of Internal Medicine and Pediatrics

Yale University School of Medicine

New Haven, Connecticut

ACTING INDUSTRY REPRESENTATIVE TO THE COMMITTEE (Non-Voting)

Christopher Smalley, PhD, MS, MBA

(Participation in March 8th AM session)

Director, Engineering Biosterile Validation

Merck & Co

West Point, Pennsylvania

C O N T E N T S

C O N T E N T S (continued)

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. I would first like to remind everyone 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. If you are present, please stand. Thank you.

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

DR. HONG: I am Cindy Hong, the designated federal officer for the Pharmacy Compounding

Advisory Committee.

DR. BUCKLEY: I'm Lenore Buckley. I'm an adult and pediatric rheumatologist at Yale University School of Medicine.

MS. BORMEL: I'm Gail Bormel, acting director of the Division of Prescription Drugs in the Office of Unapproved Drugs and Labeling Compliance in CDER.

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

DR. JOHNSON: I'm Susan Johnson, the associate director for the Office of Drug Evaluation IV, filling in for Dr. Charles Ganley today.

MR. FLAHIVE: I'm Jim Flahive. I'm a regulatory counsel on the Pharmacy Compounding Advisory Committee team within CDER compliances, Office of Unapproved Drugs and Labeling Compliance.

DR. MISHRA: I'm Shrimant Mishra, medical officer in the Division of Anti-Infective Products.

DR. HULL: I'm Keith Hull, medical officer

in the Division of Pulmonary, Allergy, and Rheumatology Products.

DR. ORLEANS: I'm Ron Orleans, a medical officer in the Division of Bone, Reproductive, and Urologic Products.

DR. MAYNARD: I'm Janet Maynard. I'm a clinical team leader in the Division of Pulmonary, Allergy, and Rheumatology Products.

DR. GULUR: Let's start with you.

MS. DAVIDSON: I'm Gigi Davidson. I'm the chair of the USP Compounding Expert Committee, and I represent USP on this committee.

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

DR. DIGIOVANNA: I'm John DiGiovanna. I'm a dermatologist at the National Cancer Institute NIH.

MS. JUNGMAN: I'm Elizabeth Jungman. I direct public health programs for The Pew Charitable Trust.

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

Practices.

DR. CAROME: Mike Carome. I'm a director of Public Citizen's Health Research Group.

DR. WALL: Donna Wall, I'm the clinical pharmacist at Indiana University Hospital in Indianapolis, and I represent NABP.

MR. MIXON: Bill Mixon, Hickory, North Carolina, non-voting industry member, industry representative.

DR. SMALLEY: Chris Smalley, director of biosterile validation, Merck Sharp & Dohme, and I am the acting industry representative.

DR. GULUR: Thank you, everyone.

For topics such as those being discussed today at this 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 six drug substances and two categories of difficult to compound drug products. On the morning of the first day, we will discuss two bulk drug substances nominated for inclusion on the list of bulk substances that may be used to compound drugs in accordance with Section 503A of the Food, Drug and Cosmetic Act, quinacrine and boswellia.

We will hear presentations from FDA, ask

clarifying questions, hear nominator presentations, hold an open public hearing, and have committee discussion and voting on each of the two substances.

This afternoon we will be discussing four more bulk drug substances nominated for inclusion on the list of bulk drug, aloe vera, D-ribose, chondroitin and acetyl-L-carnitine. We will hear presentations from FDA, ask clarifying questions, and hear nominator presentations, hold an open public hearing, and have committee discussion and voting on each of the four substances.

Let us begin. We will now have Dr. Cindy Hong read the conflict of interest statement.

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 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 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 federal ethics and conflict of interest laws, covered by but not limited to those found on 18 USC Section 208, is being provided to participants in today's meeting and to the public. FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws.

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

integrity of the services which the government may expect from the employee.

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

During this session, the committee will discuss six bulk drug substances nominated for inclusion under Section 503A Bulk Drug Substances list. FDA will discuss the following nominated bulk drug substances: quinacrine hydrochloride, boswellia, aloe vera 200 to 1 freeze dried, D-ribose, chondroitin sulfate, and acetyl-L-carnitine. The nominators of these substances will be invited to make a short presentation supporting

the nomination.

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

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

We would also 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 Federal Food and Drug and Cosmetic Act, with respect the Advisory Committee on Compounding to include representatives from the NABP and the USP. Their role is to provide the

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

With respect to FDA's invited industry representatives, we would like to disclose that Dr. Ned Braunstein, Mr. William Mixon, and Dr. Christopher Smalley 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, Mr. Mixon is the owner of The Compounding Pharmacy, and Dr. Smalley is an employee at Merck.

We would like to remind members and temporary voting members that if the discussions involve any other bulk drug substances not already

on the agenda for which an FDA participant has a personal or imputed financial interest, participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all the participants to advise the committee of any financial relationships that they may have with the bulk drug substances at issue. Thank you.

DR. GULUR: Dr. Carome?

DR. CAROME: Mike Carome. I was asked to make a brief statement. I am the director of Public Citizen Health Research Group, and I would like to disclose that Public Citizen Health Research Group has published an article on the organization's website, Worst Pills, Best Pills, advising readers that they should not use chondroitin sulfate for treating osteoarthritis because of a lack of evidence of the drug's effectiveness for that disease.

In today's session, the committee will consider six bulk drug substances nominated for

inclusion on the Section 503A bulk drug substances list as they relate to the issue of whether they are appropriate for inclusion on the list of bulk drug substances that may be used to compound drug products in accordance with 503A. These discussions will include the bulk drug substance chondroitin sulfate.

The FDA has determined that I may participate fully in the deliberations of this session of the meeting and will vote on all but the one question posed to the committee regarding chondroitin sulfate. And just for the record, I would like to state that Public Citizen disagrees with the FDA's policy, both in concept and implementation, regarding intellectual conflict of interest for invited committee members. Thank you.

DR. GULUR: Thank you.

Before we begin, I will introduce one voting special government employee who will be in a specific portion of this morning's topic. She is Dr. Lenore Buckley, Professor of Internal Medicine and Pediatrics at the Yale University. She will

participate in quinacrine and boswellia topics. We will now proceed with the FDA introductory remarks from Ms. Bormel.

FDA Introductory Remarks - Gail Bormel

MS. BORMEL: Good morning. I'm Gail Bormel, acting director of the Division of Prescription Drugs in the Office of Unapproved Drugs and Labeling Compliance in CDER, and I would like to welcome you to the fourth meeting of the Pharmacy Compounding and Advisory Committee. We had a very busy 2015, a year in which we accomplished a lot, and we are looking forward to a productive 2016.

As you've heard, over the next 1 and a half days, we will be discussing six additional bulk drug substances nominated for inclusion on the list of bulk drug substances that can be used in compounding by entities seeking to qualify for the exemptions under Section 503A of the Federal Food, Drug and Cosmetic Act. These substances are quinacrine hydrochloride, boswellia, freeze dried aloe vera 200 to 1, D-ribose, chondroitin sulfate, and acetyl-L-carnitine.

You will notice that we have a new FDA staff member who assisted with the preparation of certain presentations, Dr. Charles Ganley, who is the director of the Office of Drug Evaluation IV in the Office of New Drugs. Dr. Ganley is ill today, and Dr. Susan Johnson, associate director of ODE IV, will be presenting today on Dr. Ganley's behalf and is seated at the table.

Dr. Ganley has been designated by the OND Immediate Office to work with staff in the Office of New Drugs in the conduct of the reviews of the substances nominated for the 503A and 503B bulks lists, and to assist in preparation for these advisory committee meetings.

Where there are differences in views between the divisions, Dr. Ganley has been designated by the director of the Office of New Drugs to reconcile the different viewpoints and to provide an overall FDA recommendation. Dr. Ganley performed that function with regard to the views of two of the substances we will be discussing today, quinacrine hydrochloride and D-ribose.

We will have four presentations on quinacrine hydrochloride including one prepared by Dr. Ganley. The first three presentations will be by the review divisions that looked at quinacrine hydrochloride for three different uses, and then Dr. Susan Johnson will explain the rationale for the agency's overall recommendation. Similarly, we will have three presentations for D-ribose, including one by Dr. Johnson.

Tomorrow, we will switch to another subject that we began to discuss at the June 2015 meeting of the committee, the difficult to compound list. We will review changes to the criteria for the difficult to compound list that we are proposing, which address the recommendations of the committee from the June 2015 meeting.

In addition, we will present two drug categories that were nominated for placement on the Difficult to Compound List under Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act, metered dose inhalers and dry powder inhalers.

Again, we thank you for your participation

on the Pharmacy Compounding Advisory Committee. We look forward to a productive meeting and to working with you in 2016. Thank you.

DR. GULUR: Thank you. I would like Dr. Pham to introduce herself, who has just joined us.

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

DR. GULUR: Welcome.

I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the committee. We will now proceed with an FDA presentation on quinacrine from Dr. Mishra.

FDA Presentation - Shrimant Mishra

DR. MISHRA: Good morning. I'm Shrimant Mishra. I'm one of the medical officers in the Division of Anti-Infective Products. And I as well as two of my colleagues will present different division perspectives regarding the use of quinacrine for compounding. And these are just

some of the important members of our review teams who are involved in doing a lot of the research regarding this presentation.

Just to give you a general outline of this presentation, we're going to very quickly talk about quinacrine's physical and chemical characterization, go into a little bit of its regulatory marketing history, discuss some of the safety evidence we have both from non-clinical and clinical studies, and then we're going to divide it up into discussion of different uses for different clinical areas.

So I'll talk about the Division of Anti-Infective products, and my colleagues will be discussing uses for lupus as well as for intrauterine sterilization.

Quinacrine hydrochloride, its structure just differs very slightly from chloroquine hydroxychloroquine. It's available in a highly pure form, roughly in about 97 to 99 percent a pure form, and it's available as a yellow powder that's very stable. In terms of its regulatory and

marketing history, it's a little bit confusing, so I'll try to go through this with you a little bit slowly.

The quinacrine tablets, as a single ingredient product, they were introduced as an anti-malarial drug in the 1930s, but they were never formally FDA approved. These unapproved quinacrine tablets were marketed until 1995 for the treatment of giardiasis, tapeworm, and malaria, but then they were discontinued primarily due to a decrease in demand.

Then quinacrine, a combination tablet was approved with hydroxychloroquine and chloroquine, this is called a Triquin tablet, and that was for lupus in 1958, but this was withdrawn in 1973 for insufficient evidence of efficacy.

There was a quinacrine injection that was FDA approved in 1964 for ascites. In 2003, the manufacturer notified FDA it was no longer marketed. So what we have right now is that quinacrine is not currently approved in the United States, but oral quinacrine is compounded to a

limited extent for lupus, as we'll talk about.

So other historical uses of quinacrine, it's been used as an injection for malignancy associated pleural effusions. It's been used orally for rheumatoid arthritis, and as we'll talk about in much more detail, as intrauterine slurry in pellets for female sterilization. Also note that it's currently being evaluated for use in prion diseases as well as in certain malignancies such as prostate cancer.

In terms of some of the non-clinical evidence we have for its safety, we don't have any formal safety pharmacology studies that were performed for quinacrine. We know that there have been studies, repeat dosing studies, done for quinacrine that showed a possible cardiac and hepatic toxicity in rats.

We know that it's been positive in mutagenicity studies, so it has a positive Ames test. And in testing in Chinese hamster ovary cells, it was noted to be associated with chromosomal aberrations. So it's a known mutagen.

It readily crosses the placenta to the fetus. And if you administer it to pregnant rats and monkeys, it's been associated with fetal death. We'll talk about the carcinogenicity in rats when introduced in the uterus because that's a big part of the discussion of intrauterine sterilization.

So some of the clinical evidence that we have regarding safety, it has several dermatologic effects. It can be associated with yellowish discolorization, eczematous rash or worsening of psoriasis and lichen planus. It has several gastrointestinal effects of nausea, diarrhea, vomiting, and abdominal cramping. It's been associated with aplastic anemia with chronic use, as well as porphyria.

Neurologically, it's been associated with psychosis, restlessness, insomnia, and this can occur even with short-term use. And it's been associated with an elevated liver function test, and in some cases actual acute hepatitis.

It has some ophthalmic effects, retinopathy of course, less than some of the similar agents as

chloroquine and hydroxychloroquine. And it's been associated with corneal edema and deposits.

Now, some of these adverse effects are dose and duration dependent, as we'll talk about, particularly when you're talking about aplastic anemia, but some of them can occur with short-term use.

So as regard to aplastic anemia, historically the rates have been associated with 1 incident in 50,000, and historical mortality rates around 50 percent. However, we should note that these studies that looked at these rates of aplastic anemia were usually associated with doses of quinacrine that are greater than those that are used now for the treatment of lupus.

Also, it was noted that with aplastic anemia, it's often heralded by a lichen planus rash. So there's been some thought that if you basically monitor the patient for the development of a lichen planus rash as well as use this lower dose, as well as do CBC testing fairly regularly, you may have a lower rate of aplastic anemia than

what's been associated with it historically.

It's been associated with psychosis, especially in patients over 60 years of age, although you also see cases in pediatric patients as well. It has been associated with rashes, including lichenoid reactions, some of which have gone on to develop squamous cell skin cancer. And it's been associated with reproductive tract malignancies, and that's primarily relevant to intrauterine use.

I'll talk quickly about the infectious uses. Historically, quinacrine was used for malaria, but it was heavily used during World War II, but then it was eventually supplanted by more efficacious and drugs that were thought to be less toxic; so it's really not used to treat this condition today.

Basically at this point, historically it's been approved to treat giardiasis, but again it's been supplanted by some approved drugs, such as tinidazole, nitazoxanide, as well as off-label use of metronidazole. But you do still see it used very occasionally for cases of refractory

giardiasis.

So these are subjects who may have been treated with metronidazole initially, but they still have abdominal pain or diarrhea. And this may be in the setting of a healthy patient or a patient with immunocompromised, and they're, for whatever reason, unresponsive to the initial treatment, and then after treatment with quinacrine, they improve. But it's very infrequent, but we do see that.

It's also been used for tapeworm infections historically, but at this point it's been supplanted by praziquantel. It's no longer really used in the United States to treat this condition.

So from our perspective, from the Division of Anti-Infective Products, we do not recommend that quinacrine hydrochloride be included on the list of bulk drug substances that can be used in compounding under Section 503A of the Federal Food, Drug, and Cosmetic Act.

We realize that it's physically and chemically well characterized and that there's been

significant historical use, but we don't know really the history to what extent this compounding has been used for infectious disease uses.

From our perspective, the benefits don't really outweigh the risks for infectious disease uses, primarily because currently the use is really for non-life-threatening infections, for which alternative treatments are available, and there's also these significant safety concerns, including aplastic anemia, psychosis, and dermatologic effects.

We're really concerned that the distribution via compounding will not be associated with proper labeling that provides important safety information. So in the cases where it may be necessary for infectious disease use, we would be more -- we would consider use under an IND that could allow for provision of safety information in the setting of research use or in individual cases as opposed to through compounding. Thank you.

DR. GULUR: Thank you.

We will now proceed with an FDA presentation

from Dr. Hull.

FDA Presentation – Keith Hull

DR. HULL: Good morning. My name is Keith Hull, and I'm a rheumatologist in the Division of Pulmonary, Allergy, and Rheumatology Products. As mentioned earlier, our division is recommending that quinacrine be included on the bulk drug substances list that can be used in compounding due to its use in clinical practice for the treatment of lupus patients.

So systemic lupus erythematosus, which is more commonly referred to as just lupus, is a prototypical autoimmune disease that affects approximately 1.5 million Americans. The vast majority of the patients are female with women being affected 10 times more frequently than males, and also minority populations being affected approximately 3 times more frequently than Caucasians.

Systemic involvement, which can include all major organs, occurs in about 70 percent of cases, and cutaneous, or discoid lupus, is a variant of

the disease that can lead to disfiguring scarring, and accounts for about 10 percent of cases. Despite the disease being well characterized for over a century, there are few effective therapies, and the disease represents an unmet medical need.

There are currently only three FDA approved therapies for lupus: corticosteroids, the anti-malarial drug hydroxychloroquine, and belimubab. Off-label therapies include other anti-malarials like quinacrine and chloroquine, as well as more potent immunosuppressive therapies, including methotrexate, mycophenolate mofetil, cyclosporine, and cyclophosphamide.

The anti-malarials play a key therapeutic role for the treatment of lupus and have been used to treat the disease since 1894 when Payne first described the use of quinine in treatments to treat patients with lupus.

Quinacrine was first reported to be effective for treating discoid lupus around 1940, and the first English language report of its use in systemic lupus patients occurred in 1951 by Page in

the Lancet Journal.

This created interest in the field, and a series of larger scale studies were conducted throughout the 1950s. However, despite the reports of its effectiveness, the use of quinacrine was replaced in the mid-1950s with the introduction of hydroxychloroquine, primarily because of -- from what we can gather, from a lack of a side effect of yellowing of skin as well as the ease of manufacture of the hydroxychloroquine.

A meta-analysis of these large case series involved 771 lupus patients treated with quinacrine and described clinical improvement in about 73 to 85 percent of treated patients. The initial quinacrine doses were reported as 200 to 300 milligrams daily, with subsequent tapering to 100 milligrams daily within 1 to 2 weeks.

Daily doses of 100 milligrams, which is the currently recommended dosing by rheumatologists and dermatologists, improved tolerability but had slower time to clinical response of approximately 3 to 4 weeks.

Since this time, multiple prospective studies have been conducted since the 1980s to further support the clinical efficacy of combinations of quinacrine with chloroquine or hydroxychloroquine for treatment of cutaneous lupus.

In fact, quinacrine 100 milligrams daily is recommended treatment for subjects with systemic and cutaneous lupus in medical references and published treatment guidelines, including all major rheumatology textbooks, specialty journal review articles, and the web-based medical reference sites, such as UptoDate and Medscape.

So when considering the potential risks of quinacrine, we must also take into account the risk of the disease itself as well as the toxicities of currently used therapies. Systemic manifestations of lupus can be organ and life threatening, as well known.

Similarly, current use therapies are associated with life-threatening and serious adverse events, including death, malignancy, lung

fibrosis, aplastic anemia, bone marrow suppression, opportunistic infections, and avascular necrosis.

The anti-malarial drug hydroxychloroquine is FDA approved for the treatment of lupus and is labeled with adverse events of death, irreversible retinal damage, aplastic anemia, agranulocytosis, and thrombocytopenia.

In clinical practice, these serious adverse events are uncommonly seen, but represent a similar safety profile to those that we are concerned about with quinacrine, except notably for the absence of retinal toxicity, which is not associated with quinacrine.

So in conclusion, many older anti-malarials, including quinacrine, have been studied in lupus and are considered to be effective. And although as a class the anti-malarials have overlapping toxicity, quinacrine differs in terms of the risk of retinopathy, which is generally dose related and irreversible with chloroquine and hydroxychloroquine.

In practice, clinicians will add quinacrine

100 milligrams daily to lower doses of chloroquine or hydroxychloroquine as a way to maximize anti-malarial therapy without increasing the risk of retinopathy.

Lastly, although quinacrine is associated with a dose-related yellowing of the skin and rare reports of aplastic anemia at doses about 100 milligrams per day, the overall risks are not inconsistent with what the levels of risk are for other treatments of lupus.

So in conclusion, our division is recommending that quinacrine be placed on the list of bulk substances that could be used in compounding. The drug is physically and chemically well characterized, has a long history of use, and is currently compounded for lupus patients.

Its safety profile is not inconsistent with that of other lupus treatments, and evidence in the scientific literature supports its efficacy and therapeutic need. Thank you.

DR. GULUR: Thank you. We will now proceed with an FDA presentation from Dr. Orleans.

FDA Presentation - Ronald Orleans

DR. ORLEANS: I'm Ron Orleans. I'm a medical officer in the Division of Bone, Reproductive, and Urologic products. I'm going to talk about the use of quinacrine for intrauterine sterilization.

I'll give a short regulatory history of the product. I'll mention what the World Health Organization's technical panel has written regarding the safety of intrauterine sterilization with quinacrine. And lastly, I'll give our division's recommendation whether quinacrine should be added to the list of bulk drug substances used in compound drug products.

Quinacrine is used for intrauterine sterilization in the following manner. One dose is comprised of seven 36 milligram pellets, which are placed into the uterine cavity using a preloaded IUD inserter, which is modified. This dose is repeated monthly 2 to 4 times with the aim of causing inflammation, fibrosis, and subsequent occlusion of the fallopian tubes.

In the latter half of the 20th century, quinacrine hydrochloride was widely used throughout the world. Approximately 140,000 quinacrine sterilizations were performed from 1977 through 2000 in 34 countries. However, the procedure was banned in a number of countries due to concerns about the lack of informed consent, as well as concerns regarding long-term safety.

Regarding efficacy, the majority of efficacy data are based on follow-up of women in developing countries. There are almost no randomized clinical trials on which efficacy is based. Ten to 20 percent of subjects in the studies were often lost to follow up; pregnancy rates were not consistently based on serum or urine pregnancy testing; and various dosing regimens were used.

The reported pregnancy rates ranged from 0.3 to 3.3 percent in the first year, 1.1 to 10 percent over 5 years, and 4.3 to 12.1 percent over 10 years. These pregnancy rates do not compare favorably with surgical sterilization or intrauterine devices.

Here is a short regulatory history with regard to the intrauterine use of quinacrine. In August of 1998, the FDA conducted a safety assessment and a health hazard evaluation of a quinacrine kit for female sterilization. The following concerns were identified.

Due to its mutagenicity, there were concerns raised about the possible carcinogenicity of this agent. There were concerns regarding a lack of PK data following long-term exposure of the endometrium, and there were concerns regarding the endometrial cells, which were not completely destroyed and the neoplastic changes which could possibly occur within these residual endometrial cells. Other possible safety issues included uterine perforation during insertion, the intraperitoneal leakage of quinacrine, and ectopic pregnancy.

Based on these findings, the FDA issued a warning letter in 1998 stating that female sterilization is an unsafe use for quinacrine pellets, and that the distribution of the

unapproved pellets for this use was to be halted, and the product was to be removed from the market.

Subsequent to the 1998 health hazard evaluation due to the product's known mutagenicity, a rat carcinogenicity study of intrauterine quinacrine was conducted. The authors of this study concluded the following.

"We conclude that two doses of quinacrine administered approximately 25 days apart into the uterus of young, sexually mature rats, at dose levels equal to or greater than 70 milligrams per kilogram, increased the lifetime risk of tumor development in the reproductive tract.

"The types of tumors that developed were mostly uncommon for this strain of rat. The incidence of these tumors was dose related and was significantly increased at a local quinacrine dose that was a small 8 times multiple of the human dose of quinacrine used for non-surgical female sterilization."

In 2008, a World Health Organization technical panel reviewed the available non-clinical

and clinical data on quinacrine as a sterilizing agent, and this was their conclusion.

"Until the totality of safety, effectiveness, and epidemiological data has been reviewed, quinacrine should not be used for non-surgical sterilization of women in either clinical or research settings." To date this statement has not been updated and has not been removed.

So here are the division's conclusions regarding the use of quinacrine for intrauterine sterilization. Number one, there are significant safety concerns regarding the increased risk of reproductive tract malignancies with the intrauterine use of quinacrine.

Number two, the product doesn't appear to provide a level of efficacy that would compare favorably to other available methods used for female sterilization. And number three, the use of quinacrine for intrauterine sterilization has an unfavorable benefit/risk profile.

Therefore, our division does not recommend

that quinacrine hydrochloride for intrauterine administration be included in the 503A list. Although it is physically and chemically well characterized, and there is some evidence of historic use in compounding, nevertheless, we have serious safety concerns regarding the intrauterine use of quinacrine, especially given its unfavorable efficacy profile.

Here's a summary of OND's use specific recommendations for the 503A list. Using the oral route of administration, for lupus, yes, it should be placed on a compounding list. For infectious disease uses, no, it should not be placed on the compounding list. And using the intrauterine route of administration for sterilization, no, it should not be placed on this list.

DR. GULUR: Thank you, Dr. Orleans.

We will now proceed with an FDA presentation from Dr. Johnson.

FDA Presentation - Susan Johnson

DR. JOHNSON: Good morning. My name is Susan Johnson. I'm the associate director for the

Office of Drug Evaluation IV. As you've previously heard this morning, I'm filling in for Dr. Charlie Ganley who is ill. I'm presenting the slides that he would have presented.

The Office of Drug Evaluation IV was recently designated by the Office of New Drugs to work with the Office of Unapproved Drugs and Labeling Compliance and assist in the completion of the review of substances nominated for the 503A list.

I want to provide an explanation of where the Office of Drug Evaluation IV fits into the Office of New Drugs. There are six sub-offices in the Office of New Drugs, and I've listed them here. Within each sub-office, there are divisions based on the therapeutic indications that FDA covers for drugs, and those are the individuals that you have largely heard from at past meetings regarding indications and uses for the nominated substances.

Highlighted in red are the divisions that provided memos for quinacrine's nomination and highlighted in green is the office that Dr. Ganley

oversees, the Office of Drug Evaluation IV.

The divisions have reviewed the information and have arrived at recommendations that you've heard based on their risk/benefit assessments. As sometimes happens in the regulatory and scientific environments, they've come to different recommendations for different uses of quinacrine.

The division review memos and their presentations today have provided the division's rationale for their recommendations, and OND thanks each division for having carefully reviewed the data and thoughtfully derived their recommendations.

Because there is not one uniform recommendation from the divisions, ODE IV was tasked with reviewing the memorandum for each use from the divisions and making a recommendation to the director of the Office of New Drugs. With the concurrence of the OND director, I am presenting this recommendation to you today as the recommendation of FDA as a whole on the quinacrine nomination.

An OND memo that was co-authored by Dr. Ganley, the director of ODE IV, and Dr. Jenkins, the director of the Office of New Drugs, has been included in your background package. It provides the rationale for the OND recommendation.

As was noted earlier in the presentations, quinacrine tablets were marketed until 1995, and since then, quinacrine has been compounded for patients. I also note that approximately 1400 prescriptions were dispensed in the last year from U.S. outpatient retail pharmacies according to the available data.

With regard to the use of quinacrine for intrauterine administration for sterilization, as an anti-malarial, as an anti-protozoal agent, and for the treatment of rheumatoid arthritis, we find there are FDA approved medications or methods offering a more favorable benefit/risk assessment than that provided by quinacrine.

For the treatment of lupus, particularly in those patients with cutaneous symptoms, there are

case series in the literature that support effectiveness and show a risk profile similar to other drugs used to treat this condition.

Quinacrine is however associated with serious adverse events that were discussed earlier in the presentations. These include skin rashes, hepatic injury, malignancy, and hematologic abnormalities. In some cases, these adverse effects result in significant morbidity and potential morality.

After considering the seriousness of quinacrine's adverse effect profile, OND is concerned that prescribers of quinacrine, and particularly patients using quinacrine, may lack sufficient information about its use. Under the 503A framework, prescribers would not be limited to rheumatologists and dermatologists who may have a good understanding of the use of the drug.

OND finds that to better ensure the safe and effective use of quinacrine, prescribing information is needed. That prescribing information is not provided for under the framework

of the 503A list. The prescribing information should identify the potential for serious and life-threatening adverse effects, and include information on appropriate patient monitoring and follow-up.

The Office of New Drugs therefore does not recommend quinacrine for the 503A bulks list because of the serious adverse effects associated with the use of quinacrine. Given the serious adverse effects and lack of an FDA approved drug label to guide safe and effective use, we cannot recommend quinacrine to the 503A list.

An FDA recommendation for the 503A list could also be construed and possibly promoted by the regulated industry as an endorsement of the safety and effectiveness of quinacrine when used for any condition, not limited to the conditions discussed here today.

Placing quinacrine on the 503A list would allow any prescribers, not only lupus specialists, to prescribe quinacrine for any uses. Compounding pharmacies and websites could promote the use of

quinacrine for any conditions without much FDA oversight.

OND recognizes that quinacrine has a long history of use in the treatment of patients with lupus, particularly those with cutaneous symptoms. There is a population of patients with lupus that likely benefit from the treatment with quinacrine.

OND is committed to helping the clinical community maintain the availability of quinacrine for use in well informed and managed therapeutic situations. We recommend that quinacrine access be maintained under an IND. We further recommend that if possible, studies will be conducted with the intent of gaining marketing approval and approved labeling.

Clarifying Questions from the Committee

DR. GULUR: Thank you.

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

the presentations. Dr. DiGiovanna?

DR. DIGIOVANNA: I have a clarifying question for Dr. Mishra. So you presented a slide of the regulatory and marketing history of quinacrine that says quinacrine was approved in combination with hydroxychloroquine and chloroquine for lupus in 1958, and then it was withdrawn and that quinacrine injection was FDA approved in 1964. And then the next bullet says quinacrine is not currently approved.

The injection form that was approved and no longer marketed, does that mean it was withdrawn for some reason? Is the approval something that's time limited? I don't understand why it was approved and why it's not approved. And that relates to the issue that I think that drugs that are approved, and perhaps maybe have been approved but not withdrawn, are appropriate for being compounded.

MS. BORMEL: I can answer that because we worked to find this information out. But with respect to Atabrine, which was the injectable

product, we have no information if the manufacturer withdrew it from the market, but FDA has no information to suggest was it withdrawn for reasons of safety or efficacy. And the product wouldn't -- we don't have any information, whether it was withdrawn for safety or efficacy. They just withdrew it, the manufacturer.

MS. AXELRAD: Let me just -- so what happens is, if somebody is marketing something under an NDA, they can just decide for whatever reasons that they're not going to market it anymore. And then sometimes they'll ask to have their NDA withdrawn, and we withdraw it.

So we publish Federal Registry notices on a regular basis withdrawing products from the market because the sponsor of the application doesn't want to market it anymore, and there are some consequences of having it continue. You have to have annual reports and things like that, even if you might not be marketing it. So they just withdraw the NDA.

Then it becomes important if somebody comes

along and wants to make a generic for it, then they can ask for us to make a finding on whether the drug was withdrawn or removed from the market for safety reasons or efficacy reasons. And if we decide not, then we publish a Federal Register notice, or we would publish a notice one way or the other, indicating that finding.

Of course, if it was not withdrawn for safety or efficacy reasons, then you could have a generic. But unless somebody asks us to make that finding, we might just have a record that the NDA was withdrawn and nothing else.

DR. DIGIOVANNA: So if it was approved then, why do you say there was no safety pharmacology studies available? So how was it approved without those? Have the requirements changed? I don't understand that either.

DR. JOHNSON: That really is the reason, that the requirements have changed since the time that those were approved.

DR. GULUR: Dr. Vaida?

DR. VAIDA: I'm not sure if this is a

clarifying question, but for the intrauterine sterilization, the FDA put out something in 1998 and then WHO put out something in 2008. In the review or with the search, is there any evidence that it may still be used for this, either in the U.S. or worldwide?

DR. ORLEANS: Yes, there is some indication that it's used in isolated areas, like Florida.

DR. GULUR: Dr. Jungman?

MS. JUNGMAN: So I'm actually struggling along the same lines you are. If quinacrine was approved and it's not on the list of drugs that have been withdrawn or approved for safety reasons, why would it need to be on the list to be compounded?

MS. AXELRAD: Because it's no longer a component of an FDA approved drug because there is no longer -- we don't believe an NDA, here for it. So it is no longer a component. Just because a drug might have been approved at one time and is no longer approved, if it's no longer approved, it would have to be on the bulks list in order to be

compounded because it is not a component of a currently FDA approved drug.

MS. JUNGMAN: Okay, so you interpret the 503 language to mean it has to be a component of a current currently marketed drug?

MS. AXELRAD: Yes. Yes. And just to go a little further, as you recall, we had quinacrine on the meeting agenda last time because we were considering it as a candidate for the list of drugs that have been withdrawn and removed for safety reasons.

So it had been nominated for the bulks list here, and it was on the nominated or -- we were considering it for the withdrawn and remove list, and we couldn't establish exactly what its marketing status was because it was so complex.

So we determined at the close of the meeting that it had not -- it was not -- we had no evidence it had been marketed and withdrawn for safety reasons, so we took it off consideration with the withdrawn and removed list, and we're just considering it for the bulks list today.

DR. GULUR: Dr. Carome?

DR. CAROME: Does FDA have statistics on the incidence of psychosis and other psychiatric adverse events with this drug?

DR. MISHRA: We don't really -- we don't have actual rates of psychosis, but you can certainly find numerous case reports if you look in the literature. There are case reports ranging from patients who have hallucinations, both auditory and visual hallucinations, also just speaking abnormally, and you see it in a variety of patients.

In the PDR, I guess labeling that used to be for quinacrine actually mention that; you see it in a lot of these elderly patients. But more recently, when I look in the literature, I actually see it in a lot of pediatric patients that they've noticed, but I don't know the actual rates per se.

I think the important thing to note though is that again, that's something that you can see even in short-term use. These weren't patients necessarily who were taking it for long periods of

time for lupus, but just for whatever, a short-term infectious use.

DR. GULUR: Dr. Pham?

DR. PHAM: But was there a link to the -- was it a dose related effect? Because I wonder if its historic use was related to higher dosing. In pediatric patients, maybe the weight-based dosing is not really adequate for the drug exposure for that size patient.

I wanted to clarify the dose-related effect as well as does that psychosis exist in patients that had no previous like wartime history where it could possibly get muddled with PTSD?

DR. MISHRA: Yes. So I think they have seen it in patients who had no prior psychiatric history. In terms of whether it's dose related, I think they are using slightly higher doses for some of these acute treatments relative to, say, the lupus treatment, but I don't know if they know of a mechanism of action per se, if that's what you're asking. I think they've theorized that it has -- it's an activation of neuronal cells, but I

don't think they actually know. But if you think about some of the compounds that it's similar to, it wouldn't be that surprising to see some of those results, whether you're talking about mefloquine or --

DR. GULUR: Dr. Buckley?

DR. BUCKLEY: I was interested in the information you have about prescribing. So over 20 years, 1400 prescriptions, or about 70 prescriptions a year. Is that correct?

DR. JOHNSON: That was data for the last year. That was in the last year.

DR. BUCKLEY: Do you know how many of these -- can you tell by the way they're compounded which are used for sterilization and which are used to prescribe for -- being prescribed for infection or for lupus? Can you get any information from how they're compounded, or you can't from the data that you have?

DR. JOHNSON: Do you have backup slides? Let's see. Just one second.

DR. BUCKLEY: Because I think one of the

concerns we have is what's the public health risk and what do we know about how the drug is being used. Because I think the concern is, if it's out there, it can be used for many things. And one of the concerns is how often is it used for sterilization.

Obviously, maybe there's no way to know that, except if there's a difference in compounding for the conditions. I was just curious if you know something about if it's compounded differently. It said something about compounded in pellet form, and if you know something about it from the data that you have.

DR. NIKOLOV: So this is Nikolay Nikolov. I'm a clinical team leader in the Division of Pulmonary, Allergy, and Rheumatology Products, and we have specifically looked at this. I think we have a representative of the drug utilization review team.

But in general, these about 1400 prescriptions were an estimate for about the year. And about 90 percent of them were prescribed for

females, and primarily by rheumatologists and dermatologists. And this sort of mimics or represents the epidemiology of lupus.

DR. BUCKLEY: But there is no difference in how -- but you don't know anything about if there's a compounding difference for the treatment of lupus or infection versus sterilization?

DR. NIKOLOV: So I will leave this probably to the utilization review team.

MS. AXELRAD: Or DBRUP. DBRUP could perhaps answer about what the dosage form is that is used for sterilization.

DR. ORLEANS: It's an intrauterine pellet. Is that what you mean?

DR. MISTRY: My name is Kusum Mistry. I'm a drug use analyst in the Division of Epidemiology. The number of prescriptions that we obtained for 2015, it was based on for any indication. And as far as compounding, that information is not available. We're not able to obtain that data from the prescribing information. It's obtained for U.S. outpatient retail pharmacies as well as clinic

settings.

DR. GULUR: Dr. Mixon?

MR. MIXON: Thank you. I'm not a doctor.

DR. GULUR: I'm sorry.

MR. MIXON: Mr. Mixon.

DR. GULUR: Sorry. I apologize.

MR. MIXON: The fact that there were 1400 prescriptions through the retail prescription database collecting industry is pretty telling, what we don't know. Like you say, there is no data on compounding.

Just in my little corner of the world, I have a patient who takes 50 milligrams every other day, and has done so for the last at least 12 months, from a rheumatologist, presumably for lupus, although I'm trying to get that verified.

So I would encourage the committee to consider breaking new ground perhaps and approving this drug for a specific indication. I know that's somewhat discomforting for FDA to do that, but I believe that the industry can police that, personally. Thank you.

DR. GULUR: Dr. DiGiovanna?

DR. DIGIOVANNA: Are we just doing clarifying questions?

DR. GULUR: Just clarifying questions.

DR. DIGIOVANNA: We'll have a chance to discuss this later?

DR. GULUR: Yes.

DR. DIGIOVANNA: Thank you.

DR. GULUR: Yes?

MS. DAVIDSON: The last speaker mentioned recommending an IND. Is there an IND in place for quinacrine now, and could we potentially have some details on that?

MS. AXELRAD: No, there is not one in place now. However, before this decision would become final, as you know, this is a recommendation for the advisory committee, and we have to go through rulemaking to decide whether to put something on the list or not put it on the list. And we would have to -- that will be a long time before that would actually happen.

So there would be time to get an IND in

place before the final decision was made, if we were to decide not to place it on a list. And right now, I believe the drug is listed as part of our draft guidance as a drug that can be used for compounding in the interim while we're developing the list.

DR. MISHRA: Also, I'll just mention as well that -- so there's certainly not an IND for infectious disease uses right now. It may -- as I said earlier, it's being evaluated for certain other malignancies as prostate cancer and prion disease as well, but certainly nothing for oral tablets for infectious disease uses.

DR. GULUR: Go ahead.

MS. DAVIDSON: I have one follow-up question. What is the average turnaround on the IND process? Lupus has obviously got a better prognosis if diagnosed and treated early. How long does it take to get a patient turned around in an IND on average?

DR. JAROW: My name is Jonathan Jarow. I'm in the Office of the Center Director in CDER.

There are four types of compassionate use or expanded access INDs, which is what this would fall under. There are single patient INDs, emergency use, and non-emergency use, and then there are intermediate and treatment INDs, which are for larger populations.

So depending upon what would be submitted would determine the review time. For single patient INDs, emergency use, it's usually hours, which would probably not be the case in this setting. For a single patient non-emergency use, the average time is 1 to 2 days. And for treatment or intermediate INDs, there's a 30 day window, so that would be for a larger population.

So depending upon how this would be done would be up to the stakeholders involved. Obviously any individual physician would have the ability to submit a single patient IND for their patient and would have the characteristics that I described. However, an interested party, whether it be an advocacy group, a treatment center, or a compounding pharmacy, could submit a treatment IND,

which once that was in place could be expanded to treat a large number of patients added to it.

So this would have the benefit of having an informed consent that would be used with the patient to explain the risks of the treatment, the alternative therapies, et cetera, as found in the standard consent form.

Did that satisfactorily -- and just one more background piece. We get about 1,000 IND compassionate use or expanded access INDs per year at CDER; 99.7 percent are allowed to proceed.

MS. AXELRAD: I'd just like to ask Dr. Jarow to clarify that. So once the IND is in place, if you have one of these treatment INDs in place, how long did it take to enroll individual patients under that?

DR. JAROW: It doesn't take any time. You just basically have to use the consent form that's under that treatment IND, which would already be cleared by an IRB. And most of these use like a central IRB, but you could certainly use one of your institution.

DR. GULUR: Go ahead.

MS. DAVIDSON: And the providers under these INDs, is it limited to just one provider?

DR. JAROW: No.

MS. DAVIDSON: Let's say it is a compounding pharmacy?

DR. JAROW: No.

MS. DAVIDSON: Okay.

DR. DIGIOVANNA: I have a question about the IND issue because we continually read about the ability or to have as a consideration for not placing a substance on the ability to be compounded list that it is -- there's another mechanism available that is this IND mechanism. And I believe what you're talking about is the turnaround time for the FDA, but I don't know if it's -- if there's an ability --

I appreciate the number, that there's about 1,000 INDs per year. I don't know how many unapproved drugs that is for, but it would be really helpful I think for the committee in getting a sense of the availability versus the

unavailability being on the list or not, to get a sense as to who is getting these INDs.

Are any of these practitioners in small communities? Are all of these in academic medical centers or large groups of people who have access to IRBs and have access to the resources that are necessary to do that? So is someone in a small town who has lupus patients, for example, able to actually circumvent this? What actually happens?

DR. JAROW: Well, again it would depend upon which type of expanded access IND it was under. So if we're talking a single patient IND, then that physician or healthcare provider in a small community would have to be able to reference a product, so a compounding pharmacy that's producing it, in addition have a consent form that would be cleared by an IRB. If he or she does not have a local IRB, they can use a central IRB, and many of those provide their services for free for expanded access or compassionate use.

But that process seems difficult for a lot of people We've done a lot to simplify that

process. There's now a special form in development that has not been finalized, it's available in draft form, that caters to that specific type of IND rather than the general form that's used for all types of INDs, which looks very complicated even though you only have to fill out 7 boxes on it for expanded access.

Having said that, if an interested party, whether an advocacy group, or a university academic center, or a compounding pharmacy does a treatment protocol, then -- or I'm sorry, treatment IND, then that would make it very simple for anyone in a small town to get access to that. They just have to be aware of the existence of that IND, and that would potentially be promulgated by either the advocacy group or the compounding pharmacy, or whomever. But once they're aware of that, then they could use that as their thing, so they would then have the consent form.

DR. DIGIOVANNA: I guess my question is, one, where the information may not be available now, but I think would be of use, at least for me,

and possibly for other members of the committee in the future, to look at the results.

Who actually has gotten this who is not in an academic medical center and not in a large group in the past year let's say? Has this mechanism actually provided, for practitioners who are not in major metropolitan areas with access to all of these tools, the ability to get these medications or is it aware of it?

DR. JAROW: We don't have that kind of information.

MS. AXELRAD: We can look and see if that's possible. We obviously aren't going to have it today, but we can look to see what we can make known. But this expanded access is used in a lot of other areas, in cancer drugs, for example, and things like that. And there are many cases, I'm sure, in which people who are living, not in an academic medical center, are able to get access to some of these drugs. We don't know the extent, and we'll have to see if we can provide some kind of information about that.

DR. GULUR: Go ahead.

DR. CHAI: My name is Grace Chai. I'm the deputy director for Drug Utilization in the Division of Epidemiology II. I just wanted to make a point of clarification about the dispensed prescription data that was shown.

These are dispensed prescription transaction data that are captured from a very robust sample of retail pharmacies and mail order pharmacies. So what you are seeing are prescriptions that were dispensed for a compounded product, however the formulation that it was dispensed in wasn't available in the data that we had access to.

But we did look into the prescription data by prescriber specialty, this is by self-reported prescriber specialty, and the vast majority from 2010 to 2015 was rheumatology, dermatology, and internal medicine, the general practitioners. OB/GYN did account for 0.5 percent of the total prescriptions, so over the 2010 to 2015 period, out of the 15,500 prescriptions, they only accounted for 77 prescriptions. And these are national

estimates of prescription data.

So the vast majority are rheumatology, dermatology, and general practitioners from those dispensed prescription data. Thank you.

DR. GULUR: Any other clarifying questions? Dr. Jungman?

MS. JUNGMAN: This may bridge into discussions, so I'm happy to hold this. But when you say that FDA is committed to working with the clinical community regarding access for appropriate lupus patients, can you put some meat on that bone for me? What does that mean?

DR. JAROW: So again, the review of expanded access protocols -- or I'm sorry, INDs -- is not quite a rubber stamp. If there's a clear explanation, there's an adequate consent and clear explanation of the risks and benefits and treatment alternatives, the vast majority of the time, as I stated earlier 99.7 percent of the time, FDA agrees or allows the expanded access IND to go forward.

So having the review division already in favor of this as an appropriate treatment for

lupus, I don't see that that would be a problem. I'd suspect that there may be a compelling -- there's always the possibility that there will be a compelling individual case for let's say sterilization in the uterine application; I can't predict that. But that may be possible in an individual basis as well as for infection.

I can't predict that for certain, but obviously would be very confident in the case of where it's deemed appropriate, having tried other therapies or not being a candidate for other therapies, to do compassionate use for a patient with lupus.

Now having said that, if there's someone in development -- one of the other criteria of expanded access is that they are not a good candidate for an ongoing clinical trial. Our first priority for investigational drugs, unapproved drugs, is to have them studied, determine whether it's safe and effective, and brought to market to benefit all of the U.S. public.

So we do approve use because of, let's say,

there's not an active trial, or the individual patient can't get access, due to geography or other means, to a trial, does not meet the eligibility criteria for a trial. But in general, we prefer that patients enter that, and I don't think that would be the case in this setting. But there are other unapproved drugs that are frequently used through the expanded access that aren't in development.

MS. JUNGMAN: Just a quick follow-up. Are there others that are used with this frequency?

DR. JAROW: Yes.

MS. AXELRAD: I'd just like to add a little bit to what Dr. Jarow said, which is that if a group came forward and said that they were interested in doing this, and again because the division is supportive of this use for lupus, we would be willing to work with a group to look at the issues associated with IRB, what kind of information about the product would we need and that type of thing, to try and figure out a way to get this in place by the time it was needed.

DR. GULUR: Mr. Mixon?

MR. MIXON: Dr. Jarow, is there any allowance for not using an IRB? How much weight is put on a decision of an IRB? And I googled IRB, institutional review board, websites. And the first three hits of course are fee-for-service IRBs who -- I mean, how much weight is going to be put on the decision of an IRB?

DR. JAROW: It's actually required. For all non-emergency INDs, it's required that an IRB review the protocol and the consent form. It's an additional layer of human subject protection. Having said that, there are central IRBs that waive their fees for expanded access. We're definitely aware of that. I don't want to advertise for them.

MR. MIXON: Well, I think it would be helpful to know what those are. I perceive that this IRB process, although I don't want to short-circuit the system too much, is a huge barrier for a busy physician seeing 20-30 patients a day.

DR. JAROW: There's no question if one was

to the take the single patient approach in this, it would be more burdensome. It would not be impossible because we do have other examples of drugs that are currently prescribed through that mechanism. But if you had a treatment IND, you wouldn't have to go to the IRB for each individual patient. It would already be done.

MR. MIXON: Thank you.

MS. AXELRAD: Could we ask Dr. Jarow before you -- can you address what the benefits are of the IRB? What is the role of the IRB? It's not just something that's there to be burdensome to people. It's there for a reason.

DR. JAROW: Yes. So again, this is a layer of human subject protection. It's required by regulation that any investigational drug, and this would be considered an investigational drug, that the consent form and the protocol be reviewed by the IRB in addition to another layer of the FDA reviewing it as well.

Did that help?

DR. GULUR: Yes?

DR. HOAG: I have two quick questions. One is, you get this IND. How long is it good for? And when you say IRB, could like I open up an IRB in my basement, or what defines an IRB?

(Laughter.)

DR. JAROW: I'm not going to be able to answer all the qualifications for an IRB, but you could open up an IRB in your basement if you satisfied all of the regulatory requirements of that IRB. But having said that, what was the first part before we got to the basement?

DR. HOAG: How long is an IND good for?

DR. JAROW: Forever, until it goes on clinical hold. So if there's an issue -- so there have been cases where, through expanded access, there have been serious adverse events; let's say -- with this history of this drug, this would very unlikely be the case. But for new investigational drugs that are available through expanded access, sometimes patients die while receiving the drug, and the IND may go on hold, either temporarily or permanently.

DR. GULUR: Dr. DiGiovanna?

DR. DIGIOVANNA: I have a question for Jane. I think that almost any substance that's able to be compounded can be abused and can be used improperly. I wonder what tools we have to be able to negotiate a scenario where a compound that has great demonstrated utility can be prevented or made it more difficult for it to be abused, but permitted to be compounded under certain conditions.

We've addressed that when it came to topicals versus systemics or intravenous products, but here you have a variety of potential oral uses, some which may be standard of care and others which may be perceived as abusive.

MS. AXELRAD: Well, I think that gets to the difficulties of limiting things that are put on the bulk drug substance list by indication. And that is the pharmacist who is compounding the drug may not know what indication it's going to be used for. We've said that if it's a different dosage form, obviously if it's a topical versus an oral, people

know the difference. But if you try and limit it by indication, they may not know. So it would be very difficult to prevent its use in a way of what we're trying to prevent.

But I'd also say that, sort of stepping back at the whole exercise that we're doing here, is that Congress determined when they passed the law that it was okay, reasonably okay, to do compounding from something that is a component of an FDA approved product, or for which there's a USP monograph. And generally, those two things are -- an applicable USP monograph. And generally, those two things, they line up together.

But the drugs that we're talking about here are things that have never been or not FDA approved. They're not the subject of a currently approved application. As we've said, for things that were actually the subject of an approved application many years ago, the standards were very different then than they are today for showing that something is safe and effective.

What we're doing is a good-faith effort by

all of the reviews that you've seen to sort of take a look at what we know about these substances and to look at the combination of their efficacy, what do we know about whether they work, as well as their safety.

I think for things where we've seen that they work pretty well and we don't have safety concerns, then we have been recommending that they be placed on the list. But when you get to a substance that is not approved, even if it does have efficacy, it's used to treat a serious or life-threatening disease or condition, and it has side effects, I think what we've said consistently is that we have concerns about putting it on a list and having it be used in compounding because patients do not get adequate labeling to warn them about it. They don't have informed consent about what it is that they're getting, that it's an unapproved drug and things like that. So that's where we have suggested that the IND is the appropriate mechanism.

DR. GULUR: If we have no further clarifying

questions, we will now proceed with the nominator presentations. We have one presentation on quinacrine, Dr. A.J. Day from the Professional Compounding Centers of America, PCCA.

Nominator Presentation - A.J. Day

DR. DAY: Good morning. Thank you very much for the opportunity to come and address the committee. My name is A.J. Day with PCCA in Houston, Texas. PCCA does provide compounding pharmacies with the opportunity to acquire quinacrine hydrochloride for compounding.

Now, we've had some very lengthy and robust discussions about the various uses of quinacrine, and as one of the specific divisions within FDA has recommended, specifically for rheumatology purposes, it is not an investigational drug, it is a standard of care.

There's a robust portfolio of evidence about both the safety and efficacy, as well as how it compares with other medications, whether FDA approved or utilized off-label for the treatment of lupus.

So quinacrine was utilized in an injectable format, oral tablets. Atabrine was a brand name. This is all background that was addressed earlier. We also looked at the Triquin product, and as well as when these products were discontinued in use.

There was a USP monograph for quinacrine hydrochloride, a USP. It first appeared in 1942 in USP12. It was removed in USP23 when the commercial product was discontinued. And this was due to small market size, as noted.

There was a product on the market that was removed from the market, but if it was for safety and efficacy reasons, it would have been on the FDA's so called negative list, the products that were removed from the market for reasons of safety and efficacy.

The quinacrine hydrochloride bulk powder that PCCA does provide to compounding pharmacies meets the compendial standards of USP22. There was also a British pharmacopeia monograph as well. So when you look at the purity of being at or greater than 99 percent on the assay, and this particular

lot meeting 99.97 percent purity, that is meeting compendial standards.

Here we have the PDR from 1995 for Atabrine tablets as well as the Triquin PDR reference from 1961. And here we have the American Drug Index looking at Triquin and the composition thereof.

Really, in compounding, quinacrine is utilized for patients with lupus, most commonly combined with hydroxychloroquine to reduce the dose and dose-related toxicities of the hydroxychloroquine.

There are highlights from a recent international lupus meeting looking at the proposed mechanism of low dose hydroxychloroquine and quinacrine hydrochloride combination for long-term maintenance of lupus. Long-term maintenance. Again, as noted by the rheumatology division within FDA, you're really eliminating the ocular toxicity with the utilization of quinacrine and minimizing that with hydroxychloroquine.

Here we have the lupus conference and the trials that looked at it as a standard of care,

again, published by the organization in 2014.

Clinical utilization, this was another reference that was cited by the FDA's analysis with Wallace in 1989, and he looked at 771 patients, 73 percent average response rate.

They also go through an adverse effects profile as well as monitoring parameters. They looked at how to best take care of your patients. What should you be looking for? What are your criteria for screening appropriate patients that might be receiving quinacrine? All of this is readily accessible in published literature.

Again, there's a number of information that is available that looks at the results of quinacrine when you're treating lupus published recently, published historically, the data abounds. We talk about patients who have failed on standards of care, whether it's hydroxychloroquine or other FDA approved therapies, 67 percent being responders to initiation of a combination therapy with quinacrine. And we also have the information on its utilization from the United Kingdom.

Now, although this information says United Kingdom because of the national health system's database, it does not include Scotland, Ireland, or Wales, so it's really looking at England specifically. And it's looking at prescriptions in England that go through the government healthcare system. And you can see that the prescribing of this is quite robust.

They also have adverse reaction reports. Now, looking at data, the first reaction date reported in 1965, and the most recent in November 2015, one of them was a fatal report, 41 total ADR reports. That's fewer than one a year. And they do note that the existence of an adverse drug reaction report in this analysis does not necessarily mean that the medication has caused the reaction. So this fatal ADR report is not definitively a result of quinacrine therapy, as are the other 41.

In addition, the UK does have, as part of their national health service, patient information on how to utilize quinacrine, when is it

appropriate for a patient to be considered for quinacrine as an option for therapy. They have patient instructions on how to take it. Some of these instructions match up with what Mr. Mixon has stated for his patients in North Carolina.

The British Association of Dermatology has this is a standard of care and a recommendation as well as patient information leaflets available. So the information for patients is readily available.

Martindale is a standard reference that most pharmacists have. At compounding pharmacies, we have this on every shelf. There is a lot of data in here about the risks associated with quinacrine. We have data about dosing, as well as references to the actual studies.

They do look at various indications. I gave you here a screenshot of their information on lupus, but they do also have information on intrauterine use, which is not recommended, as well as anti-malarial therapy and anti-infective therapy, again which is not recommended due to other therapies being available.

When they address safety, they talk about the potential for transient acute toxic psychosis, which is a question that has come up here in the committee discussion. They talk about the lichenoid eruptions, which have occurred after prolonged use, and the aplastic anemia, again after long-term use. And as the gentleman from the Division of Anti-Infective Products talks about, the aplastic anemia being preceded by dermatoses.

So the aplastic anemia risk, there's a lot of discussion about what is that risk. If it's a severe risk, can we afford to expose patients to this? And we'll get to that in a little bit, but the FDA's documents themselves note that the incidence is 1 in 500,000 patients.

Now, there are a number, again, of articles. I'm not going to spend a lot of time going through the specific articles on quinacrine for lupus therapy because that has been discussed at length.

When the FDA talked about the risk of aplastic anemia, they lean heavily on the data from Gonzalez-Sixto, the 2010 published study that

looked at incidents from World War II. However, once they look at the number of cases from excessive doses of quinacrine hydrochloride concomitant drugs known to be associated with aplastic anemia, as well as the number of patients presenting with signs and symptoms that should have been caught to then discontinue therapy and prevent the aplastic anemia, they do acknowledge, and this is a screenshot from the FDA's briefing document, that the incidence is approximately 1 case per 500,000 patients or approximately 0.0002 percent.

The Journal of Clinical and Aesthetic Dermatology in January 2013 published a review article looking at all of the published literature that's available, and where does quinacrine fall in line for the treatment of lupus, what are their treatment recommendations. And you can see here that it is a second-line therapy to be combined with hydroxychloroquine or chloroquine. Again, it is second-line therapy according to this journal.

Recent studies show that combination of hydroxychloroquine or chloroquine with quinacrine,

which has no retinal toxicity, has synergistic efficacy without an increased risk of retinopathy. One hundred milligrams per day is advised as an adjuvant in patients with refractory disease, or as monotherapy in patients with ocular alterations of other contraindications to hydroxychloroquine or chloroquine.

Kuhn from 2011, again, has a specific treatment protocol to spell out for patients, pharmacists, and physicians when would quinacrine be an option for your patients.

Now, the FDA's concerns about safety and toxicity have some data behind them, so let's look at some of this data. The Division of Anti-Infective Products analysis talks about quinacrine being a DNA intercalator and potential mutagen. And specifically the quote is, "Because mutations can lead to carcinogenicity, many mutagens are considered potentially tumorigenic." And they have two reference citations, so let's look at the first one, Rotival.

So again, the specific quote from FDA says,

"Literature references indicate quinacrine hydrochloride is mutagenic as discussed further below, and clastogenic in vitro. The identified potential impurities are also possible genotoxins and mutagens."

Now, this Rotival study actually says that using computational approaches, the analysis of the potential toxicity of the impurities compared with the parent compound, one, shows that ketone and derivatives may exhibit specific toxicity profiles. This is a speculative conclusion.

They have no in vitro or in vivo data to directly show that these potential impurities actually do have genotoxic or mutagenic properties. They use computational approaches to speculate on that outcome.

Again, the specifications utilizing the PCCA pure chemical require greater than 99 percent purity. The certificate of analysis was also included in the nominator materials. And the major degradation products of quinacrine that were found in that Rotival study are generated from extreme

stress with quinacrine in an aqueous medium.

As has been discussed at length here, quinacrine is compounded in anhydrous dosage forms. Now, even in that specific anhydrous dosage form, the degradation that was found in the Rotival study for the dry quinacrine powder were not generated until it was heated to about 250 degrees Celsius. That's 482 degrees Fahrenheit, which is far beyond any temperature that the powder is ever going to be subject to in compounding or storage of the compounded preparation.

So looking at the other studies cited by the statements from the FDA's briefing document, Clarke 2001, they looked at the mutagenic and carcinogenic potential of quinacrine. This was an in vitro study using toxic levels of quinacrine on prokaryotic and eukaryotic cells. And they concluded mutagenicity on some of the prokaryotic cell lines.

This is a little bit difficult to digest because the prokaryotic cell lines, it's a bacteria, and quinacrine is known to have anti-

bacterial activity, so it should be killing some of these cells.

So there's another study which was not cited in the FDA's analysis. This is a study by Gurova where they analyzed both the Clarke 2001 study as well as 174 other studies and conducted their own in vitro and in vivo experiments. And they identify several weaknesses within the Clarke study, one of them being that the prokaryotic cells lines utilized to identify the carcinogenic and mutagenic properties, yet the quinacrine does exert anti-bacterial properties. We do expect it to kill those cells and to have an effect on their development.

Most tests on the eukaryotic cell lines showed no carcinogenic or mutagenic effect from quinacrine. Additionally, the methodology used in those analyses are considered poor quality and tend to provide false positives for mutagenicity; again, that's referring to the 2001 Clarke study. Modern testing methods used for prokaryotic and eukaryotic cells implemented by Gurova and colleagues showed

lack of carcinogenicity and mutagenicity. And your full reference is at the bottom of this slide.

Some further statements from this study and the conclusions, we found that in vitro treatment of mammalian cells with either 9-aminoacridine or quinacrine did not result in any signs of DNA damage. We used a number of standard assays for the detection of DNA damage and the results have all were clearly negative. Jumping onto the next one, finally quinacrine did not promote tumor formation in vivo as would be expected for a genotoxic compound.

The Gurova study concludes with the kind of common knowledge information that widespread administration of quinacrine to hundreds of thousands of young people for prophylaxis against malaria, and to women in many different countries for sterilization, had no frequent observed, obvious adverse consequences, including development of cancer.

Moreover, studies assessing the potential carcinogenic effect of quinacrine, which is

expected to be a direct consequence of mutagenic effect, showed that quinacrine had no carcinogenic effect on its own. In various studies, quinacrine either promoted or reduced the effects of known carcinogens, but in no case was quinacrine found to be carcinogenic itself.

Now, moving on to the DBRUP division and some of their concerns, they looked at quinacrine being a derivative of acridine and belonging to a class of compounds that are known to have mutagenic properties. Well, that Ferguson study, again, used in vitro prokaryotic methods, which have the previously described weaknesses also analyzed by the Gurova study.

They also cite an intrauterine study, the Cancel study, which had results of higher incidence of ovarian tumors in a dose-dependent manner. And this was the rats where they injected it into rat uterine tissue, most notably at a dose of 70 milligrams per kilogram in female rats.

The study does note that there was no difference in tumorigenicity from the control group

and the group that was dosed with 10 milligrams per kilogram. Now, even at that 10 milligram per kilogram dose, that is significantly higher than the 100 milligram PO dose that is used for patients with lupus. And as Dr. Orleans mentioned in his presentation, the 70 milligram per kilogram was even 8 times the dose of typical intrauterine utilization in humans.

So we have a long history of use. Human tolerance is well known with regards to quinacrine hydrochloride, over 80 years of use prior to World War II, millions of patients, well documented anti-rheumatic uses.

I'm not going to read all of the statistics that are on here, but the incidence of psychosis that was discussed in the previous clarifying question round, we have some data on that with a full citation at the bottom of the slide, 0.4 percent of toxic psychosis, the 0.0002 percent incidence of aplastic anemia, as stated in the FDA briefing document.

Now, I've got a few slides here where we

have some screenshots, again, direct statements from the FDA briefing documents. The rheumatology community has continually recommended the use of quinacrine hydrochloride for the treatment of lupus, and it is listed as a treatment alternative in the scientific literature, major rheumatology textbooks, and online medical reference sites.

Performing a complete blood count and thorough skin exam every 3 months in quinacrine hydrochloride treated patients is recommended in the medical literature to screen for potential cases of aplastic anemia. Given the safety profile of quinacrine hydrochloride, it is acceptable considering the relative safety of other lupus treatments.

In 1996, American Academy of Dermatology included quinacrine hydrochloride on a list of first-line systemic treatments for lupus. And the addition of quinacrine hydrochloride to hydroxychloroquine therapy should be seriously considered as long-term maintenance therapy of remission in patients with systematic lupus to

reduce ocular toxicity. These are 2015 studies, recent literature. The use of quinacrine hydrochloride is recommended in the most recent algorithm for treatment of systematic lupus erythematosus.

Now, I also have a number of references from the actual medical literature. This is what the dermatology students are being taught in medical school, in their fellowships, in their residencies. This happens to be the standard reference according to students of dermatology and preceptors of dermatology that I was able to contact and the specific screenshots for when quinacrine gets added to therapy. They also go through how they monitor patients and how they screen patients for appropriateness.

Again, a number of references, a number of medical citations about the utilization of quinacrine in all of your major dermatology textbooks. This is not an investigational therapy. It does not belong under an investigational new drug application.

There were some letters that were also sent in along with my presentation to the FDA, as well as one that was sent directly to the FDA from a physician. That one that you should have received ahead of time from Dr. David McLain, the executive director of the Alabama Society for the Rheumatic Diseases. He has over 241 patients currently receiving quinacrine for lupus. Again, this is not investigational, this is a standard of therapy that has been around for a long time.

Here we have physicians from Wake Forest Baptist Health. It is not only prescribed directly from community dermatologists, but it is taught in medical schools. These are prescriptions coming in from major teaching institutions.

Here we have another academic dermatologist who is concerned about the FDA's recommendation to not recommend quinacrine for the positive list, and that it must go through an IND. Full PDFs of both of these letters were sent along with this presentation, so hopefully all of your members on the committee have a copy of that.

So again, it is compounded as oral capsules for combination therapy in patients with lupus. It is recommended as first-line treatment by the American Academy of Dermatology. It is included in treatment algorithms in medical education, protocols, and literature.

Chemically stable, non-mutagenic, non-carcinogenic, and non-tumorgenic as the evidence has been provided. There's a long history of use in human populations around the world with a very well known adverse reaction profile, well established guidelines for prescribing, patient counseling, and patient monitoring. Very low incidence of adverse reactions at therapeutic dosing.

FDA presented information on the number of prescriptions dispensed in a community setting utilizing information from IMS, which really looks at prescriptions that were submitted for insurance reimbursement. It's not complete data because oftentimes prescriptions for compounds are not covered by insurance, so it does not look at actual

the number of prescriptions overall that are paid for in cash.

However, let's look at that number of about 1400 prescriptions dispensed in 2015. They do not present any data on adverse events. FAERS does not pull up any information on incidence of adverse reactions due to quinacrine hydrochloride. And the information from the UK indicates that the incidence of adverse reactions is likely to be very small.

Another point that I'd like to make is that the clarification discussion for an IND talked about inclusion criteria and when might an IND be considered. And one of the discussion points was that you have to have a patient that's eligible go through a clinical trial first. Again, this is not an investigational drug. There's nothing new about this therapy. There's nothing new about where quinacrine lies in the protocol for rheumatology and for the treatment of lupus.

So I urge the committee not to push this drug towards an IND in that the safety and the data

presented does not indicate a definitive risk for patients, and that the number of prescriptions that the FDA presented in their clarifying discussion does indicate that, by and large if not completely utilized for the treatment of lupus, the fact that 0.05 percent of the prescriptions, 77 prescriptions, in a 5-year period were prescribed by OB/GYNs does not mean that those were for intrauterine utilization. That means that an OB/GYN wrote the prescription. Thank you.

Clarifying Questions from the Committee

DR. GULUR: We will now entertain clarifying questions for the nominator from the committee. Dr. Jungman?

MS. JUNGMAN: Could you just talk about what the potential barriers might be to an organization like PCCA applying for a treatment IND as has been suggested would be an alternative?

DR. DAY: So in this meeting is the first time that we've heard that any organization can apply for an IND, for an expanded access or compassionate use IND. The information that we

have had previously talked about the treating clinician applying for the IND, and in a previous PCAC meeting, they talked about an actual compounding pharmacy applying for an IND.

If the facts are that anybody, any association or any entity, can then apply for an expanded access IND, then we'd be happy to do so. However, we still have a fundamental issue with the concept that a drug such as quinacrine is investigational. It absolutely is not investigational. It is a standard of care.

DR. GULUR: Any other questions to clarify? Go ahead.

MS. DAVIDSON: Dr. Day, your certificate of analysis that you projected, I assume that that complies with the omitted USP monograph, and that's where the specifications came from for quinacrine.

DR. DAY: Correct.

MS. DAVIDSON: So it could be stated that if a compounder obtained quinacrine substance from PCCA, that it would be of USP quality?

DR. DAY: Yes.

MS. DAVIDSON: Thank you.

DR. DAY: And that is very important because the statute, the HR 3204 DQSA, talks about the inclusion criteria for substances that can be using compounding. And they say that the substance, regarding the USP monograph, must meet the standards of an applicable USP monograph. It does not say a current USP monograph. And as I presented to you, there is a USP monograph from USP22. So whether or not that meets the criteria of being an applicable USP monograph, I don't know.

DR. GULUR: Dr. Jungman?

MS. JUNGMAN: I have another question that's probably for FDA, but it's about the presentation. Dr. Day, you suggested that had the drug been withdrawn for safety or effectiveness reasons, it would be on FDA's list, and thus we can conclude that it was withdrawn for economic reasons.

That's not actually my understanding of how the withdrawn or removed list works. Am I misunderstanding it? If no one had actually asked FDA why it was withdrawn, then we don't actually

have a conclusion about why it's withdrawn, do we?

MS. AXELRAD: Yes. If we don't have any data, we only are putting things on the withdrawn and removed list for which we have information that indicates that it was withdrawn for reasons of safety or efficacy.

If somebody just withdraws it, and we were never asked to make the finding of whether it was withdrawn or removed for safety reasons, or in many of the cases that we presented, there were press releases and documentation at the time that it was withdrawn for safety reasons -- but if we don't make the finding, then there is nothing we can use to decide now -- we've looked to see if there was anything, and there just isn't evidence associated with these withdrawals that indicates whether it was withdrawn for safety or efficacy reasons.

DR. GULUR: Go ahead.

MS. DAVIDSON: And just to clarify withdrawal, is that of the product or did you withdraw the approval?

MS. AXELRAD: Usually -- what we mean is a

withdrawn NDA, that there is no presently -- any NDA for the product, right? We have checked that, and there is no current NDA, so the NDA was withdrawn.

As I said, it's often just a, you know, the sponsor discontinues it for whatever reason, and then a few years later, because they don't want to have to like keep it up and do what they need to do, they ask us to withdraw it. And then we issue a notice in the Federal Register, You'll see long lists of NDAs that have been withdrawn, and there's no need to have any reason for that, unless somebody wants to market it for a generic, based on that NDA. Then we have to make a determination that it was not withdrawn for safety or efficacy reasons.

I also want to correct one thing also that Dr. Day said, which is that the patient to be under an IND has to be enrolled in a clinical trial. That is not true. That is not the case. I just want to make sure that you're not left with that thought in your mind because it isn't the case.

DR. GULUR: I do have a clarifying question for you. So to further affirm, now that you are aware that the IND process is open and it's something you can pursue, it would be something that PCCA would pursue?

DR. DAY: If the substance is voted to not be placed on the 503A positive list, then we will take whatever steps we can to assure patient access to a life-saving medication. If that means that we can sponsor an IND process, then absolutely we will go forward in that direction, or work with our colleagues in the medical community to do so.

DR. GULUR: Thank you.

MS. AXELRAD: Hang on one second because we want to make one clarification about the applications that were withdrawn and why they were withdrawn.

DR. JOHNSON: So to our understanding, the Atabrine single ingredient oral tablet was never approved. It never had an NDA. It ceased to be marketed in the 1990s because the company didn't have a market for it. That was the company's

decision as we understand it.

The NDA for the 3-ingredient product, hydroxychloroquine, chloroquine, and quinacrine, did have an NDA. It did have an approval for malaria and lupus. Is that correct? Just for lupus.

The NDA came into existence at a time when the organization was mandated by law to review for safety and not for efficacy. And later in FDA's history, the 1950s, we started to catch up with existing -- '62, thank you. I should know my amendments better than that.

In 1962, the organization started to review efficacy data for existing NDAs. It was found that the individual ingredients in Triquin did not have sufficient evidence of individual efficacy that they needed to use in combination.

So in other words, if you looked at hydroxychloroquine's addition to the use, to the efficacy of this product and quinacrine's use and chloroquine's use, and their benefit to the addition of efficacy to this product, that had

never been established.

There was no reason on record, in the data, that showed that you needed the 3-ingredient product. That's why the NDA was withdrawn for lack of efficacy. It doesn't mean anything with regard to the individual ingredients. It means that the combination was not justified.

Then lastly, there was a quinacrine injection product that was a sclerosing agent. It was used in ascites in cancer. It was approved in 1964 based on safety and efficacy, and the manufacturer discontinued it. They reported in an annual report that they were discontinuing it due to lack of sales, lack of use.

DR. GULUR: Dr. DiGiovanna?

DR. DIGIOVANNA: Although in fact, isn't quinacrine added to hydroxychloroquine to minimize the retinal toxicity? So while there might not be a clear-cut efficacy, there are now standard of care beneficial reduction of retinal toxicity, so that's why it's used.

DR. HULL: That's our understanding as well.

DR. GULUR: All right. Thank you, everyone. We are running a little behind. We will now have our morning break. Committee members, please remember that there should be no discussion of the meeting topic during the break among yourselves or with any member of the audience. Please return to your seats at 10:30 a.m.

(Whereupon, at 10:19 a.m., a recess was taken.)

DR. GULUR: Thank you, everyone. If you could take your seats, we will now begin the session after the break. We will now have Dr. Janet Maynard from the FDA present on boswellia.

Presentation - Janet Maynard

DR. MAYNARD: Good morning. My name is Janet Maynard, and I'm a rheumatologist and a clinical team leader in the Division of Pulmonary, Allergy, and Rheumatology Products at the FDA. I will be discussing boswellia serrata extract or BWSE. The review team for boswellia serrata extract is listed on this slide.

By way of overview, boswellia serrata extract was nominated for uses in inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, asthma, and for anti-inflammatory properties generally. This clinical review will focus on use in osteoarthritis and rheumatoid arthritis.

Boswellia is a genus in the Burseraceae family with approximately 40 species. Boswellia resins and extracts are available in the United States market as dietary supplements. Oral and topic applications of boswellia as herbal medicines are used in other parts of the world for various diseases and symptom treatments, such as arthritis and pain. This table summarizes the compendial descriptions of boswellia botanicals found in the United States, European, and Chinese pharmacopeias.

Boswellia extracts are complex, naturally derived mixtures that can vary significantly in composition. Boswellia serrata contains several main classes of compounds, including 22 to 80 percent total boswellic acids, 5 to 15 percent

volatile oils, and 10 to 40 percent other compounds, such as polysaccharides.

Boswellic acids have been considered as useful bioactive chemical marker compounds. The overall composition in a given boswellia extract is often unknown. The most common boswellic acid analogs are listed on this slide.

Literature suggests that boswellic acids are the major active components and can serve as chemical markers of boswellia extracts. However, it is important to note that the composition of boswellia extracts, as well as the total and relative proportions of boswellic acid analogs, can differ depending on the botanical source and manufacturing method.

In terms of overall quality considerations, the composition of boswellia extracts, including total content and relative proportions of boswellic acid analogs, can differ depending on the botanical source and manufacturing methods.

Good agricultural and collection practices to support sustainable production of boswellia

resin in native habits have not been established. Raw materials may vary significantly in quality. Different manufacturing processes, including various solvent extractions, have been utilized to concentrate boswellic acids from boswellia resins.

Boswellia extracts contain multiple classes of molecules so their composition is not well characterized and cannot be adequately controlled solely based on the analysis of boswellic acids. Additional raw materials and manufacturing process controls are needed to ensure quality of boswellia extracts. In conclusion, we do not consider boswellia extract to be well characterized and can be adequately controlled for compounding drug use from a quality perspective.

Animal studies suggest that boswellia serrata extract has anti-inflammatory properties, but the exact mechanism of action is unknown. There are no well designed and well controlled quality data to evaluate the toxicity of boswellia serrata extract, but no significant toxicity was observed when rats were dosed with 1,500 milligrams

per day boswellia serrata extract enriched with 30 percent AKBA for 90 days. Boswellia serrata extract was not genotoxic in in vitro and in vivo testing. The carcinogenic potential of boswellia serrata extract has not been evaluated.

Reproductive and developmental toxicity of boswellia serrata extract has not been evaluated in animals, but the Chinese pharmacopeia states that boswellia serrata extract products are not recommended in pregnant women.

In conclusion, the available information is insufficient to conduct a sound non-clinical safety assessment of boswellia serrata extract, a mixture of several compounds.

I will now transition to the clinical assessment. In terms of safety, in the literature, the most commonly reported adverse events with boswellia serrata extract were gastrointestinal, including diarrhea, abdominal pain, and nausea. However, traditional uses of boswellia include menorrhea, dysmenorrhea, and emmenagogue.

Emmenagogues are products that stimulate

blood flow to the pelvic area and uterus, and may induce abortion or prevent pregnancy. Sources suggest that boswellia should not be used in pregnancy due to these concerns. This is a significant safety concern given the potential use of boswellia serrata extract by women of childbearing potential.

Another notable safety concern is related to the potential increase in the anticoagulant effect of warfarin that could lead to adverse events related to bleeding. Reported adverse events in clinical trials include epigastric and abdominal pain, nausea, diarrhea, fever, headache, acidity, anorexia, and constipation.

The Office of Surveillance and Epidemiology, or OSE, evaluated the FDA Adverse Event Reporting System, or FAERS, for all adverse events reported with boswellia. Three cases from one literature report described drug interactions between boswellia and warfarin that resulted in over-anticoagulation effect. There were no reports of pregnancy loss associated with boswellia.

The Center for Food Safety and Applied Nutrition, or CFSAN, evaluated the Center for Food Safety and Applied Nutrition Adverse Event Reporting System, or CAERS, for adverse event reports about a product containing boswellia. 208 cases were identified.

There was a spectrum of adverse event severity, including serious and life-threatening adverse events and deaths. All of the cases involved products containing multiple components or other medications, thus no definitive conclusions were possible.

Now we will transition to consideration of clinical efficacy. We will start with a discussion of osteoarthritis. A Cochrane review from 2014 found high quality evidence from 2 studies and 85 participants that 90 days of treatment with 100 milligrams of enriched boswellia serrata extract improved symptoms compared to placebo.

This slide provides a summary of five studies in osteoarthritis that evaluated the efficacy of boswellia serrata extract for signs and

symptoms of disease. There were limitations to interpretation of these data.

For example, in several publications, there was lack of clarity regarding the efficacy findings, analysis methods, and comparisons being made. It was sometimes unclear if the publication was comparing the response rate within or between groups. Thus, there were limitations, but in general, the data suggested some patients had improvement in signs and symptoms of osteoarthritis with boswellia serrata extract.

In terms of efficacy in rheumatoid arthritis, four studies were identified evaluating boswellia serrata extract. One study did not suggest efficacy. Two studies included drugs with multiple components, so it was unclear which component might be contributing to potential effects.

One publication reviewed the results of other studies, but limited details were provided, and some studies included patients with other diagnoses besides rheumatoid arthritis. In

addition, there was no evidence that boswellia serrata extract inhibits radiographic progression in rheumatoid arthritis. Therefore, these studies did not provide convincing evidence of effectiveness for boswellia serrata extract in rheumatoid arthritis.

In summary, this compound is intended for the treatment of numerous conditions, including osteoarthritis and rheumatoid arthritis, which are serious diseases. Numerous treatments have been approved by the FDA for both osteoarthritis and rheumatoid arthritis after a demonstration of efficacy in well controlled clinical trials.

While there are limitations to the available data, there is some evidence that boswellia serrata extract may improve symptoms for some patients with osteoarthritis. There is insufficient evidence that there is efficacy for rheumatoid arthritis. Further, there are numerous treatments for rheumatoid arthritis that have established efficacy, and there's a risk of irreversible structural damage with ineffective therapies.

Historically, boswellia has been used for millennia throughout the world, particularly in Ayurvedic and traditional Chinese medicine for various therapeutic uses, such as anti-inflammatory, analgesic, diuretic and antiseptic uses.

In summary, since boswellia serrata extract is a naturally derived botanical substance, its physical and chemical characteristics can vary according to the source and extraction method. Thus, we cannot ensure consistent quality of bulk drug substance.

In terms of clinical considerations, limited safety data suggests boswellia serrata extract is generally well tolerated. However, its association with terminating and preventing pregnancy is a significant safety concern given the potential use in women of childbearing potential.

In addition, there are reports of interactions with oral anticoagulants leading to an increase in anticoagulant effect. Literature data suggests there may be efficacy in some patients

with osteoarthritis, but inadequate data to support efficacy for rheumatoid arthritis.

A number of safe and effective FDA approved agents are available for the treatment of both rheumatoid arthritis and osteoarthritis. There is historical use of boswellia serrata extract for multiple conditions.

Based on consideration of these factors, we do not recommend that boswellia serrata extract be placed on the list of bulk drug substances that can be used in compounding under Section 503A of the Federal Food, Drug, and Cosmetic Act. Thank you.

Clarifying Questions from the Committee

DR. GULUR: Thank you.

At this time we will accept clarifying questions from the committee.

DR. WALL: A question, especially with its use in osteoarthritis. Since you can't reverse the disease, we're dealing with symptomology for their symptoms. When you have gone through the regularly prescribed treatments and you either hit with it's failed, it's intolerant, they're having adverse

effects, would you be in favor, when you have run through the regular stuff, of trying something like this? Would it be a safe alternative that somebody could try to help with the symptoms?

DR. MAYNARD: So if I'm understanding correctly, you're saying if a patient has tried the currently FDA approved therapies for osteoarthritis specifically, but is having either adverse events related to those therapies, or is having lack of efficacy, would I consider using boswellia serrata extract personally for a patient.

DR. WALL: Yes, because these are the types of patients I would envision that you would -- when you're getting down to using these kinds of products, you've gone the standard route. So my question for you is just that, would you consider trying something like this? Would that be an option for a patient or, based on what you have read, it should never be tried?

DR. MAYNARD: Right. So if we're talking specifically sort of in the context of thinking about whether or not this drug should be compounded

but focusing on safety and efficacy, hopefully I highlighted that there is some suggestion that it may give benefit for signs and symptoms of osteoarthritis, but you always have to balance that with any potential safety concerns. And hopefully I've highlighted that we do have some safety concerns about the use of boswellia serrata extract.

DR. GULUR: Any other clarifying questions? Dr. Hoag?

DR. HOAG: Am I correct in assuming that this compounding list has nothing to do with products that are already on the market, like say under the DSHEA Act?

MS. AXELRAD: That's correct. You can still get it at a health food store if you want to get it at a health food store. For things that are dietary supplements that are legally marketed under DSHEA, you can still get them there.

DR. GULUR: Dr. Buckley?

DR. BUCKLEY: I was wondering if you could put the slide up again about the Cochrane review,

and if you have any more information about the studies. I was surprised -- so I think what we're saying is that it provided relief of pain or stiffness, but the size of the studies was surprisingly small, and it seemed improbable that with such small studies you would see such positive effects.

So just looking at the data, you would have to wonder were they adequately blinded? Are the numbers really believable? Were they powered to show these effects? And I didn't know if you have any more information about the studies.

The typical osteoarthritis study would not have these numbers of patients to show. For example, for an non-steroidal, anti-inflammatory require large numbers of patients, so I'm curious the numbers and the duration is fairly short duration of therapy for a chronic arthritis.

DR. MAYNARD: Right. So you're correct. This provides a summary of some of the studies that were included in the Cochrane analysis, and I did go to look at the specific studies. And as you

mentioned, they looked mainly at signs and symptoms, and there would be a suggestion in several of the studies that there was some improvement for signs and symptoms. But as you also highlighted, there were some limitations just because of differences between the studies, short duration of therapies.

So I think you've highlighted some of the difficulties in translating what is seen in these actual studies as to whether or not there's really sort of substantial evidence that there is effectiveness or evidence of efficacy of this product for osteoarthritis.

DR. BUCKLEY: If I'm looking at this slide correctly, we're talking about studies with 20 people on a treatment, 15 people on a treatment?

DR. MAYNARD: Correct. So you're right that they were small in size.

DR. BUCKLEY: Really remarkable small studies.

DR. GULUR: If there are no further clarifying questions, we will now proceed with the

nominator presentations. We have one presentation on boswellia by Ms. Kieffer from Fagron.

Nominator Presentation - Kimberly Kieffer

MS. KIEFFER: Good morning. I'm Kim Kieffer. I represent Fagron North America. We, like PCCA, also provide bulk substances to compounding pharmacies. And I'd like to thank you for the opportunity to be here today.

The FDA did a very good job of highlighting what boswellia serrata extract is. It is a plant species of the Burseraceae family, and it typically grows in regions of India. And it's active components of course are the boswellia acids that she identified.

Boswellia has been sought for its anti-inflammatory activity. In vitro study shows that boswellic acids can often block synthesis of pro-inflammatory A5-lipoxygenase products. Unlike traditional NSAIDs, boswellia acids have been shown to be glycosaminoglycan sparing.

Boswellia has a long history of widespread use in Chinese, Ayurvedic, European, Africa, United

States medicine, and it is available as an herbal and dietary supplement from many, many, many dietary supplement manufacturers. I listed a few here, but you can Google it, and there are dozens and dozens and dozens and dozens more. So this material is available in general on the market. However, it does have a USP monograph, and materials that are available commercially are not necessarily subject to these monographs.

In the USP monograph, boswellia is subject to hold not less than 90 percent to 110 percent of the label amount of extract of the boswellic acid keto derivatives. The FDA did define what those were.

In general what the USP quantifies is the 11 keto beta boswellic acid and 3 acetyl-11 keto boswellic acids, so it is defined what we are standardizing to. USP also requires heavy metal specifications, residual pesticides, loss on drying, and microbial counts.

So in terms of safety and adverse effects, FDA did already define this, but in clinical

trials, it's generally well tolerated and animal studies reflect no signs of toxicity or mutagenicity, however carcinogenicity studies are not reported. It is associated with gastrointestinal adverse effects, including diarrhea, abdominal pain, et cetera. This is consistent with other therapies.

Interaction with oral anticoagulants has been observed, but again this is something any time a patient that is on an anticoagulant therapy, adds a new pharmacological therapy or dietary supplement in their regime, this is something that will be monitored.

I've also made a table of the available safety data or of the efficacy data. This is not by any means all that is available in the literature, but these studies were either double blinded or randomized double-blind. We do see a small cohort of patients and the relative lengths of time that they were studied were small, but in most of the cases we did see statistically significant pain reduction as compared to placebo.

We have already looked at these so I'm going to go on. But one in particular that we looked at was Vishal et al. It was a randomized prospective where they studied the effects of boswellia versus valdecoxib, which would be a standard therapy. And at one month, the study did favor valdecobix therapy in terms of effectiveness, however at 7 months, we saw a higher favorite trend towards the boswellia. So that showed that it is as effective as the valdecoxib and perhaps even having better effect.

Then, I also wanted to point out two other studies that are not necessarily on osteoarthritis, though that seems to be where it has the most effective data. In a randomized controlled study, they looked at the effects of boswellia on diabetic patients for its anti-diabetic effects.

What we found in this study is that there was significant increase in HDLs, decrease in blood cholesterol, LDLs and fructosamine with no adverse effects. And in most of these studies, we observed no or low adverse effects.

This is also interesting in the next study to show that patients with chronic colitis were randomized into two groups to either receive boswellia 3 times a day or to receive sulfasalazine 1 gram 3 times a day, which would be the standard therapy. In 6 weeks, the study showed that the boswellia was actually as effective as the Sulfasalazine. So again, these additional studies are showing its overall anti-inflammatory effect.

So my conclusion is simply this. It's well tolerated in clinical studies. There is fairly extensive efficacy data to support its anti-inflammatory activity. Boswellia is available as a dietary supplement from many vendors, but remember, this is without quality verification and monitoring.

Compounding can provide formulations with USP monograph material that are from FDA registered and inspected facilities. Compounders can also, through their vendors that supply these materials, verify chain of custody and country of origin. They can also be presented with an allergen

statement and other transparent information regarding the chemical. This is something that cannot be obtained from something that is obtained through online transaction from Amazon or through Whole Foods.

Yes, these things are available, but compounding offers the opportunity for the physician to not only verify the quality of the product, but also to give the patient specifically what the patient needs. In some of these cases, the patient may not be able to swallow the capsules from the Whole Foods, and they may require a chewable tablet or an oral suspension. Compounding pharmacy has an opportunity to take care of the patient in that manner.

Also, when a compounding prescription is prepared, the physician and the compounding pharmacist are then taking care of the patient. This information regarding the safety and efficacy of this particular product and other dietary supplements is available in the literature, Martindale's, DRUGDEX, AltDEX. This information is

there and patients can be counseled on it.

For this reason, I ask that it be considered for the bulks list. Since it is going to be commercially available anyway, this gives the physicians some absolute opportunities to create a specific dosage form and regime specifically for that patient. Thank you.

Clarifying Questions from the Committee

DR. GULUR: Thank you. We will now entertain clarifying questions for the nominator from the committee.

MS. JUNGMAN: How do you go about assuring yourself of the quality of your bulk substance given the concerns that were identified by FDA?

MS. KIEFFER: From a manufacturer's standpoint? There is a USP monograph for this material, so it is tested to meet that. When we purchase materials from a manufacturer, it comes with a certificate of analysis giving us those verifications. Once we receive it in-house, we then send it out to an independent testing facility to verify those terms.

MS. JUNGMAN: And just to be clear, that's a dietary supplement monograph, is that right?

MS. KIEFFER: I'm sorry?

MS. JUNGMAN: It's a dietary supplement monograph, right?

MS. KIEFFER: It is a dietary supplement monograph. There are two?

MS. DAVIDSON: Two.

DR. GULUR: Dr. Davidson, if you could clarify that. There are two monographs?

MS. DAVIDSON: Certainly, there are two USP dietary supplement monographs for boswellia. There's one for the extract and one for the pure substance from the tree.

MS. KIEFFER: Correct.

DR. GULUR: Dr. DiGiovanna?

DR. DIGIOVANNA: Those are dietary monographs, exactly yes. So they're not the kind that will allow --

DR. GULUR: Dr. Buckley?

DR. BUCKLEY: Just a clarifying question about the studies you cited. Some of them were

randomized, some of them were not. In studies that talk about pain, blinding is very important because it's a subjective report. Were the randomized trials blinded? In other words, did the person --

MS. KIEFFER: No, not if I didn't specify.

DR. BUCKLEY: They were not blinded?

MS. KIEFFER: I indicated when they were.

DR. GULUR: Dr. Davidson?

MS. DAVIDSON: And I don't know if you know that the IUCN has listed boswellia species on the vulnerable and threatened list. What steps does your company take to ensure that the sources are reasonably harvested for this product?

MS. KIEFFER: Actually, our company doesn't sell boswellia any more. In actual reality, I don't believe that this material is being compounded that often. In fact, it was something discontinued because we don't in fact sell it any more. It wasn't being purchased.

But we did nominate it when this process began because we were selling it. And we really are here to speak out and ensure the options for

physicians if this is something that they want to use. And the reason that we have these products on our product offering is because physicians are asking compounders to prepare them for them.

MR. HUMPHREY: Do all of the companies that provide the bulk substance ensure the same quality that PCCA does?

MS. KIEFFER: Well, I can say for my company they do. I can't speak for everyone.

MR. HUMPHREY: But there's nothing that would prevent a compounding pharmacy from purchasing it from a supplier that does not meet those standards, correct?

MS. KIEFFER: There is not, but there is a minimum requirement for bulk suppliers. We have to be FDA registered, and we have to be purchasing from FDA registered facilities.

DR. GULUR: Thank you.

MS. KIEFFER Thank you.

Open Public Hearing

DR. GULUR: We will now proceed to hear open public hearing speakers. I will read the following

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the product, and if known, it's direct competitors.

For example, this financial information may include the payment by a bulk drug supplier or compounding pharmacy of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning

of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair. Thank you for your cooperation.

The open public hearing portion of this meeting is now open.

DR. WERTH: Thank you for the opportunity to be here today. I have no financial conflict of interest, and my comments have been reviewed and endorsed by the American Academy of Dermatology Association. The AADA represents more than 13,500

U.S. dermatologists, many of whom use quinacrine to treat patients with lupus.

So by way of background, I attended Johns Hopkins. I have my medical boards in internal medicine, dermatology, and immunodermatology. I participated in a lupus clinic at NYU in the rheumatology division prior to moving to Penn in 1989. I have an appointment in both dermatology and rheumatology at the University of Pennsylvania. I practice and research many patients with problems related to autoimmune skin disease. I'm listed yearly in Top Docs magazine, and I also co-wrote some of the textbook chapters that were previously mentioned by Dr. Day.

I have many grants in the area of autoimmune disease, including from NIH, the VA, as well as a number of lupus foundations listed there. And I performed the first investigator initiated studies for cutaneous lupus and amyopathic dermatomyositis, and I developed outcome measures to help facilitate some of those trials.

I'm also co-founder of the Med Derm Society,

the Rheum Derm Society, initiated the combined internal medicine dermatology residency program in the U.S. I'm chair of the Standards of Care Committee for the Medical and Scientific Committee of the Lupus Foundation of America. And I also am involved with the Myositis Association and work with international myositis groups on myositis response criteria and outcomes.

I have had a number of longitudinal databases for my lupus patients over the last 8 years with over 400 patients that I've been following as well as over 200 dermatomyositis patients.

Quinacrine is normally added to hydroxychloroquine when it hasn't worked for skin disease and lupus, and also dermatomyositis patients, and fully one quarter of my lupus patients are on quinacrine, and 33 percent of my dermatomyositis patients are on quinacrine.

Quinacrine is also used not just by myself but also by rheumatologists around the country for systematic complaints including arthralgias,

arthritis, fatigue, and pleuritic chest pain. Quinacrine is also used for other autoimmune diseases when other therapies are not working.

I have worked very hard to develop a disease severity measure so we can look at how well our therapies are working in the skin in lupus. These are some of the validation studies that we've done. These are the kinds of patients that we're confronted with on a daily basis, and we need the best therapies that we can use for these patients.

In one single center cohort of our patients that were prospectively examined with our disease severity tool, we found 55 percent of patients in our cohort responded to hydroxychloroquine, so that leaves a lot of patients who don't respond. And of the ones that don't respond, we found 66 percent of the patients who entered our database prior to starting quinacrine responded when we added quinacrine to hydroxychloroquine.

This just shows you some examples of patients on the left who were responders and how quickly they responded. And the non-responders

even on the right were also trending down, although not significantly.

So quinacrine by history was made until 1993, as we heard about earlier today. And when they decided to stop making the drug, the patients began to flare as they ran out of the drug. And that was true for many of us around the country, and we scrambled to find ways to provide medication for our patients.

We located compounding pharmacies, which had been able to be the mainstay of providing this treatment to our patients since that time. And recently, many insurance companies have actually stopped paying for quinacrine, which is yet another problem, which I'm not here to talk about today, but it's a testament to the efficacy of quinacrine that many patients now pay for the medication out of pocket.

So quinacrine is on the list of all published treatment algorithms by lupus experts and it includes again the quinacrine we're talking about by the AAD. And also, it's part of the

standard of care in continuous lupus algorithms that have been discussed and developed by the Rheum Derm Society.

I recently participated with the Alliance for Lupus Research where quinacrine was actually number one at the top of the list of recommended drugs or repurposing for lupus during a recent review of over 150 drugs.

So it stated that there are good alternatives, and so here we have a list of the anti-malarials. There's hydroxychloroquine, which is still going to be available. If we add quinacrine to hydroxychloroquine to those who don't respond to hydroxychloroquine, that would be considered next. And then chloroquine might be switched to if the hydroxychloroquine doesn't work and we continue quinacrine.

So we're told there are many good alternatives, and I've outlined what they are here. There are chemotherapy drugs, such as methotrexate, mycophenolate, mofetil, and azathioprine. We have thalidomide, and we have biologics.

So what are the issues with these alternatives given that approximately half our patients don't respond to hydroxychloroquine? Well, with the chemotherapy drugs, there's a risk of infection and malignancy. They don't always work. They need extensive blood monitoring. And it's not fair I think if we have an alternative for our patients let's say if we're not to be able to use that.

We have thalidomide, which is teratogenic, and 25 to 50 percent of our patients get a peripheral neuropathy. And we have the biologics, which are costly. Typically, the studies have not been done in cutaneous lupus patients, only in SLE, so we can't even access those for our patients. They have side effects. They're often not oral, and they're not always effective.

So what about quinacrine safety? It's used in many thousands of patients. No one can recall a single case of aplastic anemia from quinacrine among the groups of rheumatologists and dermatologists that I've spoken to over the last

year at the doses that we use for autoimmune disease, which is different than what's been used in the past.

We do monitor and we monitor CBC and hepatic tests as quickly as one month after starting the drug. And again, no problems we've seen with aplastic anemia, but rarely we do see increased transaminases, which are easily reversible when the drug is stopped. We don't see eye toxicity, which is really important because the other alternatives such as hydroxychloroquine can cause eye toxicity. And it's the only alternative for patients with diabetes, macular degeneration, or who are intolerant to hydroxychloroquine.

You can occasionally see a different type of drug rash, yellow color or pigment deposition in the skin, but this is reversible with stopping the drug. And many feel that it's safer than almost any available medication, including hydroxychloroquine.

The cost is quite minimal. The monitoring we do at a month. And although we continue to

monitor, we don't see abnormalities after that point. And if it's unavailable, then large numbers of patients who benefit from the drug will have problems. It will be difficult to care for our refractory patients without escalating to more toxic therapies. The options are really significantly more toxic.

We will see significant flares of skin and systemic disease. We saw that before in 1993. And it will be increasingly difficult to care for these patients. Already insurance companies are not covering compounded meds, medications are not being manufactured, and the options are less safe, more costly, and not necessarily effective.

Many rheumatologists, dermatologists, and patients are appalled at the potential loss of this safe and effective medication. Why do you want to remove this drug? Thank you very much.

DR. GULUR: Mr. Mixon? We have some questions for you if that's okay.

MR. MIXON: Yes, ma'am. Thank you. I'm sorry, I missed your name. Do you have any

experience obtaining medications through the expanded access program? The FDA's expanded access or compassionate plea program.

DR. WERTH: No, I do not. Can you explain what that would be?

MR. MIXON: I'm sorry, can I tell you what it is?

DR. WERTH: Yes.

MR. MIXON: Well it's a program that FDA offers as an alternative for obtaining medications. And it's been suggested that perhaps the expanded access program is going to be a mechanism that FDA will -- or that we will use, or FDA will use, to make this drug available for patients like yours.

The big unknown is exactly how burdensome that is for the practitioner that are trying to take care of patients like you and I am, which is why I asked the question.

DR. WERTH: Yes. I mean, I can tell you already there are huge amounts of effort that are expended to get these medications for patients, and we should make it as easy as possible.

MR. MIXON: Do you work in an area that has an institutional review board?

DR. WERTH: Yes.

MR. MIXON: Well, that's one of the barriers right there, that for you at least would be potentially minimal.

DR. WERTH: So I mean, I think the issue would be even with an IRB, and if you get an IND, if the drug is really that unavailable, it will be very difficult to obtain. Yes, you can probably get it that way, but one would need reimbursement for the time and effort required. And I think individual patients -- I haven't gone that route with other drugs. I can assure you the amount of time it takes is enormous. And it really would be a huge burden on people around the country I think who are taking care of these patients to try to go that route.

MR. MIXON: Well, that's what we're all trying to understand. Thank you.

DR. GULUR: So I have a clarifying question for you as well. As a physician, very familiar

with the IRB given your studies, et cetera, and having the access, as Mr. Mixon pointed out, and the thousands of patients that are being treated with these medications per your notes and what we've heard, again, we would like to understand what the barriers are.

It appears that you weren't completely familiar with the process itself, but if you were made familiar with the process, is that something you would pursue in order to maintain access? And would that have an influence on the fact that it's not currently reimbursed because it's not an approved drug, but going the IND route might actually make it more accessible to your patients because it could be paid for?

DR. WERTH: So I think again it would depend on what level the IND is offered. If it's done at a company level, if it's done by the pharmacy association, then I think that would facilitate people having access around the country. But practitioners are really burdened down right now, and to expect them to put in INDs and so on and to

get IRBs is I think not a good way to take care of patients.

DR. GULUR: Any further clarifying questions?

(No response.)

DR. GULUR: Any other public hearing speakers? I apologize. We have one more question.

DR. HOAG: I'm just curious, in your clinic and experience, how many prescriptions do you think are filled a year for this drug?

DR. WERTH: So as I mentioned, 25 percent of my lupus patients, I have 400 in my prospective database, so it's probably hundreds of prescriptions each year for patients. And I'm not doing it because I'm making any money from it but because my patients benefit from it.

DR. GULUR: Thank you. Any other public hearing speakers? Please introduce yourself.

DR. CHONG: My name is Ben Chong. I am from the University of Texas Southwestern Medical Center, and I think I also submitted slides, but hopefully they will be there, too.

I'm in the department of dermatology. I also have a clinical -- I do not have any financial disclosures to release as well. I have a clinical research interest in autoimmune skin diseases, particularly in cutaneous lupus, and have had all extensive experience working with quinacrine in prescribing to my patients as well.

I've also had the chance in an academic center to also train multiple residents and fellows in the use of quinacrine who are now currently actively using that in their practices, whether that's in academics or in the community as well.

Like Dr. Werth had mentioned earlier, I also have a prospective database of patients with cutaneous lupus where we do look at patients, how they do over time with the different medications including quinacrine.

This paper has been mentioned before, but I also just wanted to mention how lupus has been used -- actually quinacrine has been used quite extensively in lupus patients. And a couple things I just wanted to make sure I highlight in this

review.

This medication has been used since the 1940s, and 771 patients have been described to use quinacrine, and about 73 percent of these patients actually had an excellent or an improved response with quinacrine. It is thought that quinacrine can be beneficial for patients, lupus patients, who have skin involvement, but also with constitutional symptoms such as fatigue and fever. And like as mentioned before, it also seems to have a synergistic effect when it's also used in combination with hydroxychloroquine.

Many of us dermatologists and rheumatologists end up using this medication for treating lupus patients and also dermatomyositis patients. And when local treatment such as topical and intralesional steroids are not helpful, we often resort to systemic treatments, and the first line usually is low-dose prednisone and the anti-malarials, including hydroxychloroquine, quinacrine, and chloroquine. And prednisone is not really a long-term option, so we end up going to

the anti-malarials.

Up to 40 percent of patients actually do not really respond to hydroxychloroquine, or don't tolerate it for other reasons such as retinal toxicity. So the other alternatives are chloroquine, which unfortunately is not currently available in many of the U.S. pharmacies, and then quinacrine as we've talked about before.

As Dr. Werth and others have mentioned, there are other treatments which are more second line, including mycophenolate, mofetil, methotrexate, and azathioprine have higher side effect profiles than the ones that we talk about in terms of anti-malarials such as quinacrine.

So quinacrine is a well tolerated medication, has had an extensive use since the 1940s. Three million American military personnel actually took this medication up to four years for malarial prophylaxis, and at that time, the deaths were mostly due to overdoses, which we typically do not now use. And there have been not been any reports of immunogenicity or genotoxicity in these

patients as well.

In my experience, I currently have 30 patients who are on quinacrine as well, and again, it's well tolerated. Only two patients have mentioned that they could not take quinacrine again, and these were again mild symptoms, including headaches and stomach upset. I also readily practice monitoring guidelines by doing CBCs and LFTs to make sure that these patients are closely monitored.

So I just wanted to highlight a couple patient cases of people who have been on quinacrine and have benefited largely, and I'm sorry that the photos may not necessarily be as obvious. But this is a patient who has discoid lupus that's predominately on the scalp.

She had partial benefit from hydroxychloroquine, but she was still having quite a bit of redness and itching and irritation from the skin lesions that were on her scalp. And we placed her on quinacrine 100 milligrams daily, and within a few weeks she did develop decrease in her

symptoms, decreased redness, decreased itchiness.

We kept her on for about 13 months, and then she finally was able to get off of it. What I also wanted to note was this was a patient who was a little bit a higher risk who had a history of beta thalassemia as well. But because we followed her blood counts very closely, she was still was able to tolerate the quinacrine treatment quite well.

The second patient here is also another patient who was also placed on quinacrine. She also didn't have quite a bit of -- she did not get very good benefit from hydroxychloroquine either. And when we placed her on quinacrine 100 milligrams daily, she also felt better -- or she also noted better decrease in her symptoms in terms of redness and itching.

But also she had complaints of fatigue and she also noted that the quinacrine also was beneficial for that. And she's a patient who's been on quinacrine for about three years now, and I've had a hard time actually trying to get her off of the quinacrine because she's really very adamant

that the quinacrine has really benefited her quite greatly.

So in conclusion, I just wanted to highlight again that quinacrine has been helpful for many of our autoimmune diseases in skin, such as cutaneous lupus. It does have a very benign side effect profile, and it has been very -- it is considered a very safe alternative for patients who do not respond or cannot take hydroxychloroquine.

Finally, withdrawing this medication would actually put all of our cutaneous lupus patients who are currently on this medication at higher risk for disease flares and worsening. Thank you for your time.

DR. GULUR: Any clarifying questions? Yes?

DR. WALL: A quick question for you. You didn't mention in your presentation what you were monitoring is for the safety -- we talked about the efficacy, the safety of these patients. Can you give me a general overview as to when you put them on, these patients, how you monitor for the side effects and the problems that could arise?

DR. CHONG: Thank you for that question. I'm sorry that I went through that fairly quickly. But when we do put our patients on quinacrine, I do monitor them on a monthly basis initially with a CBC with differential and liver function tests. And that usually is within the first three months that we do that.

Then generally, because that's the highest risk -- theoretical risks for seeing blood counts going down. And then they usually spread that out to every three months thereafter. And that's something that we regularly teach our -- typically teach our residents and fellows on how to monitor those side effects for quinacrine.

DR. WALL: Thank you for especially talking about what is being taught in some of the schools as to how you monitor for this. Thank you.

DR. GULUR: Mr. Mixon?

MR. MIXON: Dr. Chong, do you have any experience using the expanded access program?

DR. CHONG: No, I do not.

MR. MIXON: Okay, thank you.

DR. CHONG: But I do want to add that I think, just like what Dr. Werth has mentioned as well, we do go through a lot of paperwork as well, just explanations to the patients on how to access quinacrine. So there's quite a bit of, again, I think a lot of paperwork and time that's involved already in getting patients with quinacrine.

I think if it does end up being an IND, it goes in the IND route, it does actually cause a lot of -- probably even more stress to the physicians and the providers, especially on the communities who don't have ready access to an IRB board to be able to get quinacrine for these patients.

DR. GULUR: Just to clarify that last comment, would the FDA like to comment -- am I to understand that your understanding is an IRB would be required for every patient treated with quinacrine?

DR. CHONG: No, no, not currently. But I'm saying that if you guys were considering it going down the IND route, my understanding is that that would have to be approved by local IRBs to be able

to use the quinacrine. Is that correct?

DR. GULUR: Would the FDA like to clarify that?

DR. JAROW: So that would be correct if you did an IND for individual patients, so individual patient access INDs. If a treatment IND was opened, you would not have to go to the IRB for each individual patient.

DR. CHONG: Okay. Well, I think that in some ways I think if it was an individual case, I think that would be really problematic not only for academics but even more so for a community of providers who we've been teaching as well in getting that medication for patients.

DR. GULUR: If you had access to a treatment IRB, or if you could apply for a treatment IRB given the number of patients you have on it and how strongly -- obviously we have a lot of academic leaders here advocating for it, could they get together to apply for one?

DR. CHONG: I certainly think that would be an option that we would be open to.

Committee Discussion and Vote

DR. GULUR: Thank you very much.

All right. Thank you very much.

The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. We will now begin the panel discussion portion of the meeting. We will start with quinacrine. Dr. Vaida?

DR. VAIDA: We mentioned about the indication based, and that really doesn't carry an weight with the FDA or something it can't do, but specifically with the quinacrine. But we have limited the route of administration before, haven't we?

MS. AXELRAD: I believe that yes, we have, you have recommended limiting the route. For example, for tranilast you voted to allow it to be on the list for topical use only.

DR. VAIDA: Correct. And something like quinacrine we could say oral use only.

MS. AXELRAD: Quite --

DR. VAIDA: Okay.

MS. AXELRAD: -- possibly you could do that. I think there would be -- there might be some issues with quinacrine associated with -- I mean you could say for oral use, but if you did a tablet and they chose to use it for sterilization vaginally, I'm not sure how anybody could control that. But, you know what I mean, you could certainly say orally. You could attempt to do that through the oral route.

DR. VAIDA: Thanks.

DR. GULUR: Dr. DiGiovanna?

DR. DIGIOVANNA: Yes, John DiGiovanna. So from my perspective, this shouldn't be a difficult assessment. We heard from Dr. Mishra that this drug was approved in two different formulations. There was a USP monograph for it, and it was not removed from the market for safety reasons.

Clearly, it's the standard of care worldwide. And I don't believe I've heard in any of our meetings in this committee a presentation of more convincing bulk of evidence supporting efficacy and safety from any of the substances,

including those that we've placed on the list.

Clearly, we have a packet, almost a little booklet, of experts who've testified, who treat this drug in tertiary medical centers that not only is it widely used, but they passionately feel that it's essential to the care of a certain subgroup of their patients, particularly lupus patients.

So what is the risk of not allowing it to be compounded? So who loses from that? Well, it's the patients that have the rare manifestations that aren't easily able to be treated by standard drugs. It's not likely a pharmaceutical company is going to invest to sponsor such an endeavor.

Who is prescribing it? We've heard from the FDA that 99.5 percent of the prescriptions between 2010 and 2015 were prescribed by rheumatologists, dermatologists, and internal medicine physicians; and 0.5 percent by OB/GYNs who, in my limited experience, are often for women primary care providers, and I would think many of those might also be used for the indications that were described by Dr. Hull.

So the individuals that might be harmed by this because of either a lack of efficacy or even worse, failure to have a medication that's spares the retinal toxicity, we've heard that predominately these diseases, for example, if I were to have lupus, I would probably go to one of these experts for treatment. But the likelihood is that I wouldn't have lupus because it occurs 10 times more commonly in women than it does in men. And in minorities, 3 times more commonly in minorities.

So I think it makes reasoned sense to consider who is being affected if this isn't available. Generally, the house of medicine is looking more towards precision medicine and identifying those patients who selectively need unusual either genetic or even available drug medications.

So I think we need to be thoughtful in the risk of actually not making it available, and the difficulty that it would pose for the populations that are in smaller environments, treated by local

physicians, that really wouldn't have a practical ability to obtain it.

DR. GULUR: Dr. Carome?

DR. CAROME: So in an ideal world, this drug, which appears to be efficacious, it seems to me with appropriate support an NDA could be put together with evidence to support FDA approval of an approved version, formulation of this drug. And that would be ideal, where we have a drug that's been reviewed and approved by the FDA based upon evidence supporting its safety and efficacy, where it's made by manufacturers according to good manufacturing practices, and where it's prescribed by practitioners who have available to them appropriate FDA approved labeling that describes and instructs practitioners on how to use the drug safely for appropriate patients. And that's really what's needed here.

It seems like this is a relatively large population who could benefit from this drug. I worry that when we allow compounding as a sole source for a drug, it becomes a disincentive or it

undermines the marketing forces that might lead to a drug company putting in the effort to do an NDA, and that's really what's needed here.

I think that we have certainly a number of academic practitioners at major medical centers and universities where they have the resources and are more than capable of putting together a treatment IND without too much effort that once approved by the FDA could be used by anyone across the country. The oversight that would occur with compounded drugs made under a treatment IND would be better than what we have now.

DR. GULUR: Dr. Pham?

DR. PHAM: So I want to clarify the IND because I think we keep calling it the treatment IND. And in that case I think, for those of us who do have exposure to that process in an academic setting, it can be cumbersome. There's emergent, non-emergent.

But I think what we need to really start clarifying is the intermediate size patient population expanded access because from what I can

readily find on the FDA website, the treatment IND is probably more geared towards things that are going to market or kind of in study, whereas -- I'm just going to read it straight.

"Whereas, the IND applications for intermediate sized patient populations can also be used for an approved drug that is no longer marketed for safety reasons or is unavailable through marketing due to failure to meet the conditions of the approved application," which I don't know if the quinacrine falls under, "or the intended investigational drug contains the same active moiety as an approved drug product that's unavailable through marketing."

So again, I know that there were lots of discussions about it being approved before. Either way, I feel like this quinacrine -- correct me -- seems like it would be a very streamlined, direct candidate for the intermediate sized patient population expanded access because it does actually fulfill that criteria, compared to what we're -- we keep saying treatment IND, which I feel like there

was the four -- it was like and, and, and, versus this is or, or, or. And so it seemed like we should be calling it the intermediate sized patient population if there is a barrier to the single patient use.

DR. JAROW: So this would apply to any for -- well, I'm sorry, not to the emergency use single patient potentially. But this would apply to any of those categories.

So the intermediate versus treatment, you're correct. Historically, treatment INDs have been opened on drugs that are finished their phase 3 trial, show tremendous effects, been talked about at national meetings, there's a big hue and cry to get access to the drug while the company is putting together their NDA and FDA's reviewing it. So that allows for broad access to an unapproved drug at that stage of development. But that would not preclude you from doing the same thing with quinacrine.

So with quinacrine, if some party, whether it be a patient advocacy group, or an actual

compounder, or one of those academic centers, could open a treatment IND, have that reviewed by their local IRB once to make sure that the consent has adequate -- and the protocol has adequate protection for human subjects, or the patients, their welfare, et cetera. And then people can be added on to -- any doctor could be added onto that as a sub-investigator who wants to have access to that treatment IND.

What this would basically serve -- so it would take the same amount of time for dermatologists to then do that as they do for a consent for a skin biopsy that they do in their office, so it would involve a consent. And this would replace basically what you have. In an approved drug, you have labeling for the physician and you have labeling for the patient, patient medication guide or patient medication information. So this consent would serve to replace that in this setting.

DR. PHAM: So just to expand on this point though, the reason why I am clarifying this is

because in some of the things that we're reading, particularly from the American Society of Health System Pharmacists, there is a paragraph where they say if quinacrine is not added to the 503A list, we recommend that FDA establish a regulatory pathway for making quinacrine available to patients who may benefit, and that the expanded access IND process, suggested by the Office of New Drugs and discussed in our June meeting, will not facilitate access without significant revision.

So I don't know if they're looking at the intermediate sized patient population, if they're still looking at the larger -- the single patient or the bigger treatment IND. But it feels like -- even one particular advocacy group mentions that they would hopefully pursue this regulatory pathway.

On top of that, as I go through this packet, I am counting five large advocacy groups, ASHP, Alliance for Lupus Research, Lupus and Allied Diseases, American College of Rheumatology, Lupus Foundation of America, as well as those that were

writing from academic centers, UPenn, Oklahoma Medical Research Foundation, Cedars-Sinai, Hopkins, NYU Langone, East Alabama.

So I can't imagine that of these 11 places, no one's going to put in for an intermediate sized patient -- I mean, I think that the unique thing in this particular conversation is as we talked about expanded access before, it felt like single patient use is the big barrier and the time involved is very tedious.

If you can put -- if you can frontload that into some sort of effort where there's actually that much demand coming from the public now, that this is actually the area where we think the intermediate sized patient population could be successful, unlike where we had a lot less widespread news and therefore probably going down the single patient route.

So I feel like that conversation needs to be strongly considered because this is probably the first time we've seen this outpouring of support from big groups and centers in an IND process that

might actually fit that need.

Going back to the comments respectfully submitted in the public hearing about the tedious nature of going through risk benefits and documenting all that with your patients -- and I think that's really great that those conversations are happening.

Again, one of the potential benefits of doing this is how we consider a benefit of a multicenter study where you can actually streamline your resources, maybe do something a little bit more standardized, controlled from institution to institution, gather valuable information, and then have a standardized consent so not everyone has to like do their home-grown way.

So ultimately, it seems like a lot of work maybe to go to your local IRB, but hopefully in the long run, that level of standardization actually makes life easier.

DR. PHAM: Dr. DiGiovanna?

DR. DIGIOVANNA: So I have two comments. The first is about, since you mentioned the skin

biopsy, I spent a number of years in an academic medical center at Rhode Island Hospital and Brown Medical School, and I can assure you if we wanted to tap into someone else's consent, that our IRB would have quite a bit to say about it and have to review it.

So any research that was done in an academic setting had to be approved in our academic setting there, surely. And certainly, it isn't a matter of just one consent, because every year it has to be re-reviewed, and so you do have to go back to do that again. So it isn't an inconsequential amount of time and effort. Certainly, if it's done in a multicentered way, it could be set up and you actually can accomplish that.

However, the second part of my question really raises the question to me, is what are we doing here? Are we trying to convert every potential compounded drug into an IRB roadmap where that's the only way that they are available?

In which case, I'm really not quite sure why we're listening to all of this information about

efficacy and risks and trying to make a judgment about them if it becomes only a matter of everything should be placed into that scenario.

So I think that is an appropriate alternative in certain situations, but my understanding of this committee was that since we were being given information about efficacy and risks and toxicity, that some of these substances would be appropriate to be on the bulk substances list, and should have been a result of the analysis of the efficacy and the risks.

As I said, as other people have said, this is one where there's an enormous amount of efficacy, more than 75 years' worth of experience, and really very little toxicity. So I'm a little bit clouded as to how to make that judgment.

DR. GULUR: I know there are some counter remarks there, but we're going to allow Dr. Buckley.

DR. BUCKLEY: I just wanted to add a couple of prospective comments to the excellent comments of the public speakers and the FDA, just as a

treating physician. It's already been said that this is a chronic illness, an illness of 90 percent female.

I think it's important to point out that this is a young person's problem, and it goes on for decades. And it's, as we're already said, a very serious condition. And many of these young people are going to -- maybe 50 percent are going to end up being on significant immunosuppression.

I think it's also important to say that it's very prevalent in the minority community. So it's women of color, men and women of color, but predominately women of color, and they're often people who have trouble because of their age and their ethnicity and their racial background getting access to care. And they are often people we are treating during their childbearing years.

But our alternatives for medicines, as has been pointed out, have many problems in terms of teratogenicity. So mycophenolate, which the FDA is telling us to be careful of, which is the drug we commonly use; methotrexate, another drug that's

pointed out, is problematic. So these drugs, the alternative drugs, all have significant problems.

I also want to talk a little bit about the difference between serious skin disease where quinacrine might be used as a first-line therapy and more systemic disease that the rheumatologists treat, where quinacrine is usually not used as a first-line therapy; hydroxychloroquine is.

The anti-malarials as a class are a critical treatment for lupus for a number of reasons. First of all, they're incredibly safe, and they can be used in women who are getting pregnant and they can be used in children. And they are not only helpful for skin disease, but they're helpful for mild lupus, moderate lupus, and severe lupus.

So there are good studies that tell us that if we do need to -- there are base therapy, but if we need to add immunosuppression, we end up using less. And the longer we use them, the better people do. So if someone is on hydroxychloroquine or an anti-malarial, and we add an immunosuppression, if we wait a year or two, we can

often begin to take away the immunosuppression, leaving that base of the anti-malarial.

But there's increasing evidence -- we used to think retinal toxicity was relatively rare. We quoted 1 in 10,000. Now with better ophthalmological detection techniques, we're realizing that number is an under-estimation. So increasingly, rheumatologists and dermatologists are beginning to have to take away hydroxychloroquine. And when we do, we are faced with having to up the immunosuppression and losing control.

So I think this really -- I've been in this position, many of the other physicians in the room have been in this position, of losing a really critical therapy. When we talk to our patients who have lupus, and many of them with serious lupus, what I usually tell them is their anti-malarial is their lifelong therapy. We have to get them off the corticosteroids, which have very bad side effects. We want to get them off the immunosuppression. But the anti-malarial therapy

is the base. It's the safest therapy we have, which doesn't mean it doesn't have toxicity.

So we have hard choices here. Every medicine we give people has significant toxicity. But the lack of -- I think the average rheumatologist is not going to use a lot of quinacrine. I think for severe skin disease it's going to be a more important alternative. But to not have the alternative and to have to use strong immunosuppression is a problem. And it's not going to save us from having to use drugs that are going to be a real problem for pregnancy, or teratogenicity.

If we don't have this drug, we are going to end up -- we're always talking to lupus patients about birth control. You know, I joke with my patients, the women who come in. The first thing I say is how are you, and the second thing I say is, "And just by the way, you're still using your birth control regularly?" Because almost for all the medications we use, regular discussions about contraception are going to be important.

So there are issues here about how do we give access and maybe how do we relook at this IND process. I don't know where that's going to go.

I can tell you that, as we learn more about -- as we treat people for 10 years, and 15 years, and 20 years with hydroxychloroquine, we're going to find that that's not going to be an option for some patients. And we're going to need another option, and more immunosuppression probably will be the best one.

I hope we're going to have better drugs, but until we do -- and we really don't yet. The average person with severe lupus is on two, three, four drugs for control. And losing any of these drugs is a problem. So I think just some things to keep in mind as we think about chronic care.

DR. GULUR: So Dr. Pham, Dr. Jungman?

DR. PHAM: So just a couple comments in response to the previous. I think why this conversation is as long as it is, if we had only heard from Dr. Hull, I think this would be a very simple conversation. Right? But the fact of the

matter is there's multiple indications that we have gathered information on, and previous conversations from this committee have been about how can you approve something for bulk compounding and still be able to control what's going to be indicated for or marketed for.

So it's because there are three very distinct specialty groups that have different levels of that safety and efficacy data for those specific indications. So if it was just Dr. Hull and his team and it was about CLE, I would be on board. There would probably be very minimal discussion right now, especially with the advocacy groups and the public hearing comments. But because there is not that same recommendation coming from infectious disease, as well as with the industry, I feel like that's why we're having discussion.

So when it comes down to limiting access, it's not that we want to take it away from the CLE patients, it's that we're trying to make it available with these very informed discussions to

patient provider.

Going back to the toxicity and the teratogenicity, compared to mycophenolate, mycophenolate as an approved drug is in the REMS program, and you have to have that conversation with the patient and go through that REMS process. Whereas, in the same concern for teratogenicity with quinacrine, we can't.

I'm sure that the providers do, and it's great that they're being properly educated to, but there's no such standard prerequisite way of doing that prior to dispensing that product to that patient.

DR. GULUR: Dr. Jungman?

MS. JUNGMAN: So I was going to make a very similar point, but at the risk of being repetitive I'll make it anyway. Which is I do think it's important to keep in mind that this 503A list is a really blunt instrument. So if we were just considering this substance for use in lupus, it is a different conversation.

The fact that it is chronic I think does

raise questions about whether given that, we should be looking at a process that involves consent and kind of some of those protections anyway. But I think that's a harder conversation.

If FDA puts this substance on the 503A list, then it can be marketed with drug claims for any use. And I agree with Dr. Pham that that really is what creates the difficulty in considering this substance. So I'll add that.

DR. GULUR: Mr. Mixon.

MR. MIXON: I just want to add that once a patient's in an IRB -- IND, sorry -- they can't be charged for any of the therapy, so somebody is going to have to fund that program.

DR. JAROW: That is not true. They can be charged for the drug.

DR. GULUR: Thank you for that clarification.

MR. MIXON: Thank you.

DR. GULUR: Ms. Wall, did you have a question?

DR. WALL: I appreciated Dr. Buckley's

comments. I'm looking at these patients and I keep thinking we're all boiling down to safety. Even with the IND, what does it boil down to? It boils down to very serious discussions with the patients as to what is the risk associated with any medicine we give them. And I don't care if you've got a REMS or what you got with it, it needs to be the role of the physician, the prescriber, and the pharmacist to have these discussions.

As for limiting its use, we've seen that you can put any drug on the market and the use just explodes in all other areas. So that's something we can't even accomplish with things that have been approved by the FDA. But I think we just really, as professions, need to focus on the fact that we have to have serious discussions with our patients about what are real adverse events and to educate them and to work with them so that we can handle any medicine that they give.

DR. GULUR: Yes?

DR. SMALLEY: So I want to acknowledge you know a lot of what's already been said. Certainly,

in reference to an ideal world, it would be -- I think it would be ideal if a pharmaceutical company was willing to market this, but I am actually familiar with the decision that Sanofi Winthrop made at the time because it was basically a profit decision. It wasn't profitable enough for the company.

Even at this point in time, I don't think the marketplace would support a pharmaceutical manufacturer putting this out. I think it represents an important role for compounding pharmacies to provide to meet this service.

I certainly appreciate the argument for the IND and the alternative for the IND. But I struggle with the fact that from the evidence, this appears to be an important tool in the toolkit in the therapy for a particular disease state. And it strikes me, despite the efforts to describe how the IND process can work -- and I am familiar with the IND process because I was at one point director of quality for a pharmaceutical research company -- that it is still a hurdle.

I struggle with the concept of putting a hurdle up in front of access to any important medication where in balance, the benefits seem to significantly outweigh the risks, especially from some of the public comments that we had heard.

DR. GULUR: Thank you. I will take this opportunity to restress that this is the panel discussion portion and is limited to committee members only.

Any further comments or discussion from the committee members? Dr. DiGiovanna?

DR. DIGIOVANNA: Yes, the only comment I would make is that there was a concern about the use of quinacrine outside of the generally accepted efficacy. And it's the FDA's own data that suggests that almost essentially all of it, 99.5 percent of it, was actually used by physicians who are not likely to use it for anti-infectives or for sterility type purposes.

So it seems that it hasn't been abused, at least from 2010, as far as the data to suggest. So it does seem to be that the actual use of it is

consistent with what we've heard.

MS. AXELRAD: I think a lot has been said about what was said about the drug utilization data and who is prescribing it, and I would like to have a person describe exactly what this says.

DR. GULUR: Grace, thank you.

DR. CHAI: This is Grace Chai, the deputy director for drug utilization in the Division of Epidemiology II. From the period of 2010 to 2015, for the 15,000 prescriptions that were dispensed approximately, the primary prescribers were rheumatology, dermatology, and then internal medicine and general practice. So they accounted for the majority of use.

So rheumatology accounted for 57 percent of those prescriptions, and dermatology accounted for 14 percent, and then the rest accounted for smaller proportions.

I just wanted to add one more point of clarification in regards to a comment that was made during the nominators' presentation. These are dispensed prescription data, so they also include

cash payments prescriptions, and all other forms of payment, including commercial third party.

DR. GULUR: Thank you. Dr. Vaida?

DR. VAIDA: Just one more question for the FDA on trying to limit the route. We did, as was mentioned, set some products only for topical or that, but none of that's come to fruition yet. So if we did say like oral or topical or that, what would be the recourse?

MS. AXELRAD: Well basically, we're here to hear your recommendation. You're going to vote however you would like. After you do that, we will take it under advisement and decide what we think.

So for example, with regard to tranilast, you recommended that it be used for topical use only, and we need to -- and are considering your recommendation and deciding what we're going to propose in the proposed rule.

So we want to hear what you recommend, and whatever you recommend, we'll take it into account. We've tried to say -- we think that recommending a limitation of use by indication would be a problem,

would be particularly difficult, but that we could consider figuring out how to do it by dosage form or something that a pharmacist could actually know how it's going to be used and be held accountable.

Because basically what you're talking about is allowing the use by any compounding pharmacy. You're not going to have a limited source of it. You're not going to limit the source of who they purchase it from. You're not going to limit the source of who makes it, or what percentage, or how much of a dose they get.

I also wanted to note from the drug utilization figures that although the majority, I think it was about 70 percent -- she has the exact numbers -- of people are dermatologists and rheumatologists, that leaves 30 percent who are not, who are some other specialty who may or may not be familiar with the side effects of the drug.

Also, I think you also said there are basically no side effects, and I think you really need to look at the FDA reviews because one of the major reasons that in the face of the data that

suggested this might work well in cutaneous lupus, there are significant -- there are data that raise questions that aren't mine and concerns about the side effects. So it was the weighing of the benefits and the side effects that have us proposing not to put it on the list.

So it isn't that there weren't none, and if you wanted to hear some more about that, if there was time, from our people who looked at the side effects and toxicology, for example, we could do that. But the review covers it pretty much, and it does discuss that that's one of the major reasons why we're proposing not to put it on a list.

MR. HUMPHREY: I have a question about the finiteness of an IND. We have expanded access and treatment INDs all the time, but they're usually for a drug that a pharmaceutical company is working on that we hope will eventually become commercially available.

With quinacrine, for example, we don't think there's going to be a pharmaceutical company that's ever going to market this drug, and we've heard

this is a chronic disease that we may treat for decades.

Could we say we're going to open this IND for this drug and then have it -- you know, we're going to use it for 20 years?

MS. AXELRAD: Well, medicine develops, too. Hopefully -- you don't know for a fact that there won't be other treatments that are going to be developed that are better than any of the things on the market. Yes, there may not be an NDA for this one, but again, you're looking at where we are today in terms of people, the number of patients that need it. It's not a huge -- it's a large number, but not a vast overwhelming number.

Again, the purpose -- what we're saying is that we think that because of the side effects of this drug, the patients need to be monitored. They need to be advised that what they're getting is a drug that hasn't been FDA approved. They need to be aware of the side effects through the informed consent process. And the source of it can also be controlled through an IND.

So for those reasons, we think that it should not be available for it to be freely compounded in order to protect people so that they can get the benefits of the drug, but know what they're getting and reduce the risks that they'll get side effects through monitoring.

DR. GULUR: Dr. DiGiovanna?

DR. DIGIOVANNA: I'd just respectfully like to suggest that the FDA, the part of the FDA that takes care of patients that have lupus, the rheumatology people, suggest that it should be placed on the list, and that those who have specialties that take care of other diseases where it tends to not be used are the ones who feel that it should not be placed on the list. And the ones who feel it do are the ones that have personal experience with the risk and benefit ratio.

DR. GULUR: So I would like to just make one comment here in the discussion as well. I think we all agree that the indication for lupus is strong, it's being used, and the safety and efficacy data is available for review. The concern that all of

us are facing, I think most of us are facing, is that we also recognize that there are two other specialty reviews that do reveal that there are significant risks to the population if they were utilized for something other than the lupus as an indication.

Limiting patient access is definitely the biggest concern here. I think it's been repeated many times. However, what we would like to understand better, and I know we've talked about treatment INDs and intermediate INDs amongst everything else, but it would be great, with the risk of repetition, if the FDA could summarize for us that if this medication is not on the list, what is the best process to maintain patient access through a process that would ensure better monitoring for these patients.

DR. JENKINS: Yes. Hi. I'm John Jenkins. I'm the director of the Office of New Drugs, and you heard earlier I co-signed the memo from FDA recommending that this not be on the list.

I think we struggled with this just as the

committee is having a very rigorous discussion because this is an example of a drug that may have some evidence of benefit in a serious disease, such as lupus. It also carries serious toxicity risk, and we try to balance where to fit that into the compounding schema.

You've heard that it has been used in other diseases besides lupus, but clearly we don't think the benefit/risk calculation in those other areas warrant this being available in the compounding arena.

I think there's been some minimization of the risk of the drug over the course of the discussion today. I think our expert toxicologists clearly conclude that this is a mutagenic compound, and in rodent studies it clearly was a carcinogenic compound.

There was some minimization of that earlier, but I think it is really important to understand expert toxicologists at FDA have reviewed this on numerous occasions. It was reviewed by our carcinogenicity assessment committee who agreed

that this is a mutagenic compound, and it is carcinogenic when applied intrauterine in rodents.

So we looked at this very carefully. As far as the issue of two different groups saying no, one group saying yes, we discussed this with our center director, Dr. Woodcock, who is a rheumatologist. And she concurred with our recommendation that given the risk associated with this drug, the toxicity associated with this drug, it would be best to limit the access to the IND process where you can ensure that the appropriate patients are receiving the information that they need as far as informed consent, understanding that this is not an approved drug for the use that it is being used for in their situation. And I think you've heard from Dr. Jarow that there are mechanisms through which the expanded access IND process can be utilized to make this available to those patients without it being available on the bulk compounding list.

So we considered all these issues. We discussed them extensively internally within the FDA all the way to the center director level.

Dr. Woodcock is a rheumatologist, and she concurred with the recommendation that it not be on the list.

DR. GULUR: Thank you. Would someone -- again, just to repeat this question, would we be able to understand, in a few sentences, how the FDA would recommend the IND process be followed since there was some discussion of different types?

MS. JUNGMAN: Could I just add to that? I don't think -- I don't know if you felt like your question kind of completely got answered, but we are talking about -- can you also just talk about how long that lasts? Because I think that was an outstanding question.

DR. JAROW: So we can't make an official recommendation of how it be done. The simplest, if I was on the other side, if I was a rheumatologist who wanted the easiest, least burdensome approach, would be if someone opened up a treatment expanded access IND. That would be the least burdensome.

Now having said that, we have other diseases in which -- for instance irritable bowel syndrome,

where there are drugs that have been having access for many years on single patient approach, and we haven't heard that that's particularly burdensome. I'm not suggesting that for this, but you have multiple pathways.

It doesn't have to be one treatment IND. There could be multiple treatment INDs opened up by various stakeholders or people with interest, and then physicians or healthcare providers participating in any number of those.

So again, there's not a recommended pathway. All of them would work and be applicable to this setting. But the least burdensome would obviously be a treatment IND. There have been treatment INDs where there are literally thousands of patients in that one treatment IND.

In terms of how long it would last, we talked about that earlier. As far as FDA regulation is concerned, the IND is opened until it's closed. So it would have to be withdrawn or there be a safety signal that would prompt FDA to put it on clinical hold.

What was mentioned earlier is also true, there are IRB regulations in part 50 and part 56 that would require yearly assessment of how patients are doing, updating of the consent form if new information was available through the safety reporting that takes place within an IND. But this is a very old drug, and it would be unlikely that there would be significant changes in the near future.

DR. JENKINS: This is John Jenkins again. If I could just address, there seems to be an assumption that no one is going to develop this drug for commercial use, and I don't think we should assume that to be the case.

If there is this level of widespread use through compounding for lupus, and if people believe that the evidence is there to support that there may be evidence of efficacy and a positive benefit/risk ratio from literature reports, then it is possible that someone could choose to submit an application.

You might not submit an application today

because it's widely available through compounding, but if it's not on the list, that may prove to be the incentive that someone needs to bring an application to bear.

The other advantage of having this under an IND is that you can actually collect useful information that might help to support the efficacy of the product. Most of the evidence that we saw presented were from the '40s, '50s and '60s, mostly case series versus more modern evidence, and then we heard clinical practice utilization.

So I don't think we should assume that no one would show interest in developing this as a commercial product. If the data are there, we've seen other examples where companies are willing to go into a niche market and develop an FDA approved product.

We know that today there's a lot of interest in companies developing drugs to treat rare diseases, and this would qualify probably as a rare disease. So just as you're thinking it through that, I think it's not safe to assume that we would

never see someone showing commercial interest.

DR. GULUR: Thank you.

We will now end our discussions on quinacrine and start our discussions on boswellia. Committee members?

(No response.)

DR. GULUR: If everyone is discussioned out, then we will now end our discussions on boswellia 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 vote 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 withdrawn or remove 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.

Starting with the first question, vote yes, no, or abstain for each question. FDA is proposing that quinacrine hydrochloride not be placed on the list of bulk drug substances that can be used in pharmacy compounding in accordance with Section 503A of the FD&C Act. Should quinacrine hydrochloride be placed on the list?

If you vote no, you are recommending FDA not place the bulk drug substance on the 503A bulks list. If the substance is not on the list when the final rule is promulgated, compounders may not use the drug for compounding under Section 503A unless it becomes a subject of an applicable USP or NF monograph or a component of an FDA approved drug.

Any questions?

(No response.)

DR. GULUR: Begin the vote now.

(Vote taken.)

DR. HONG: Okay, question 1 on quinacrine, we have 5 yeses, 6 noes, and zero abstain.

DR. GULUR: We will start the individual member comments, and we can start with Mr. Smalley

at the end, once we're done voting.

DR. SMALLEY: So I suppose I'm disappointed at the no votes. I appreciate all the comments that were made about the IND process and the need to provide labeling, but as was mentioned earlier, healthcare professionals do perform an important role. So that's all the comment I have to say.

DR. GULUR: Ms. Wall? Dr. Wall?

DR. WALL: I voted for it to be on the list. I think that by doing patient education, both from the practitioner and from the pharmacist, you can accomplish the things that need to be. And from what I've heard from the practitioners and reading things, I believe that there is good information that they know how to monitor these patients.

DR. CAROME: Mike Carome. I voted no for the reasons articulated and FDA's Office of New Drug decision memo. I think this is a drug, although there's evidence of efficacy for lupus, discoid lupus in particular, I think given the drug's safety profile, that this is a drug that would best, from a public health standpoint, be

best used with more oversight than just allowing it to be compounded freely by any compounding pharmacy. And that either a new drug application with eventual approval or use under an IND would be the most appropriate way to go forward.

DR. VAIDA: Allen Vaida. I voted no for many of the same reasons. I do have to say this was probably the toughest vote that I've had since I've been on the committee with this. And I probably would have recommended oral only, but I don't know if that would even restrict it to lupus use. So I voted no.

DR. PHAM: Katherine Pham. I voted no for it to not be placed on the list due to the toxicities, of the mutagenicity, the aplastic anemia, the possible psychosis, and due to the potential continued availability through an intermediate sized patient population expanded access program.

I'm hoping that from the record of the discussions from this meeting when it's made public, that a lot of these large stakeholder

groups will pursue that route. And also hope that the FDA also makes that information very visible with the context of this meeting as well.

MS. JUNGMAN: Elizabeth Jungman. I also voted not to add it to the 503A bulks list. I thought there was a reasonably compelling case made about the usefulness in lupus, but I'm concerned about the safety profile.

I'm reasonably comfortable that the rheumatologists who have experience with this product would be able to appropriately monitor these patients and convey the risk to patients, but I'm concerned about other uses. And my understanding is once we put this on the bulks list, it could be used for anything, so I'm concerned about that.

I remain concerned about availability for lupus patients, so just wanted to emphasize that I don't view this as a vote to take this product off the market, but to limit to availability through the IND process where we can ensure that we've got appropriate consent and that we're collecting data.

DR. DIGIOVANNA: So in medicine, we are increasingly trying to be what's called evidence based. A lot of times, we like to look at our own evidence and wear glasses to not see what's outside of that. And to have seen that the guidelines from many of the established medical experts who treat these patients from multiple textbooks and literature has established this as a standard of care makes it a little disappointing to see that it's going to be limited.

Perhaps it's likely that it will be unavailable to some vulnerable populations who may not have access to it. I do think that it would be nice if there was a way for us to be able to take substances that could be placed on the list and limit their use in a way that we would not be so arbitrarily restricting availability to populations that need them.

MR. HUMPHREY: I voted yes and for many of the same reasons that Dr. DiGiovanna stated.

DR. HOAG: This is Steve Hoag. I voted no. And I guess my thought was that it is easier to put

something on the list than to take it off perhaps. And I think that we should monitor this situation very carefully if there is a situation where patients are not getting access to this medicine, that we should reconsider it, because I was almost a flip of a coin going either way.

So although I think that we had a lot of discussion of the IND program, and I think this is a good program, but I don't think it's well understood and it is not clear to a lot of people. So I think the FDA should work hard to make sure that people in the field are aware of what can be done using this compassionate IND program.

MS. DAVIDSON: Gigi Davidson. I voted yes that it should be added to the list because I don't believe I heard an answer to Dr. Gulur's question about what will happen to the real patients behind the 15,000 prescriptions that have been written for this drug in the last six years. I also have concerns about the IND program, and that comes up over and over again. Dr. Werth, and we've heard others express that the IND doesn't seem to be an

ideal way to take care of patients.

The other thought I have is that any of the people who presented and petitioned today could easily petition USP to reinstate the monograph, and then we would not be having this conversation. It would automatically be something that is available to be compounded without limitation.

So I view this as an opportunity to do as many have suggested and put it on the list, limited to oral use only, and to 100 milligram strength maximum.

DR. GULUR: Thank you. I voted not to put it on the list for reasons that have already been stated, mainly because we cannot limit indications on this bulk list, and there are serious concerns if this was used for purposes other than for lupus. And I would second what has already been stated that it would be very beneficial for the medical community and our patient population at large if the FDA would explain this process and make it more easily accessible to providers who wish to apply through the expanded access IND process.

DR. BUCKLEY: I voted yes because of my concerns about the harms to patients who are already on the drug or might need it in the future because of their lack of access. And I thought that was greater than the harms that might occur to people for whom it's prescribed inappropriately. I agree there are harms to this drug, but I think they're probably a bit inflated.

I would say that I was also a little disappointed. I think the individual -- as a practitioner, I am familiar with the individual IND. And as those of us who practice, we spend a lot of time just getting drugs that are approved through insurance barriers. It's very difficult to get them for patients.

I was a little disappointed. It's clear that I think the FDA thinks that this drug is appropriate for certain populations. And having thought about the IND approach, they didn't help us think a little clearly about another not individual IND process, but a more group IND process that might have helped us all not try to think through

it real time, but think through it ahead of time in a way that would have gotten us maybe to an easier place today.

But not having had that done for us, I thought that access for patients with real illness who are going to be harmed by lack of access to this drug was a bigger problem than the public health issue. So that was my vote.

DR. GULUR: I would like to read in a clarification. My script read incorrectly. Voting will be on the two drug products just presented. All vote questions related to whether these products should be included on the 503A list. And again, it is for the two products discussed this morning.

Moving on to question 2, vote yes, no, or abstain for this question. FDA is proposing that boswellia not be placed on the 503A bulk list. The question is, should boswellia be placed on the list?

(Vote taken.)

DR. HONG: Okay, question 2, we have zero

yeses, 11 noes, and zero abstain.

DR. GULUR: We'll take voting member comments at this point. Can you start with you, Dr. Wall, yes.

DR. WALL: I voted no. The company even took the drug off the market because there just doesn't seem to be a market for it. It is on the store shelves and people can buy it. But I think that we need to look at things beyond -- especially in the area of osteoarthritis, when you look at the products that are recommended, which are even -- I believe they had even mentioned chondroitin and opioids, we need to really look at what our options are and to give patients options to deal with the symptoms with this disease.

DR. CAROME: Mike Carome. I voted no for a variety of reasons, including the variability in the composition and quality of the product that's used to make these compounded drugs, limited efficacy data, and there are numerous FDA approved alternatives that have been shown to be safe and effective for the proposed uses.

DR. VAIDA: Allen Vaida. I voted no for many of the reasons that were already stated.

DR. PHAM: Katherine Pham. I voted no for similar reasons as well as the increased risk of drug interactions with anticoagulants.

MS. JUNGMAN: Elizabeth Jungman. I voted no because of quality concerns, the limitations in effectiveness data, and the fact that there are multiple alternatives available.

DR. DIGIOVANNA: John DiGiovanna. I voted no because I agreed with the FDA presentation.

MR. HUMPHREY: William Humphrey. I voted no for the same reasons.

DR. HOAG: Steve Hoag. I voted no. These are actually very complicated products, and it's very difficult to control the quality in a pharmacy situation. And if you were actually going to send out samples for analysis, that's like $200, $300 per sample, so I wonder if people would really do that.

MS. DAVIDSON: Gigi Davidson. I voted no. I believe there are, as stated, multiple

alternatives. And I heard from one of the presenters that this is probably not commonly compounded anymore. I was concerned about the safety signal for it being an abortive agent. And not the least, I was also worried about the threatened status of the raw material plant.

DR. GULUR: This is Padma Gulur. I voted no for reasons already stated regarding quality, safety, efficacy, and the fact that there are multiple alternatives available.

DR. BUCKLEY: Lenore Buckley. I voted no because of the quality and efficacy data, didn't think it was convincing.

Adjournment

DR. GULUR: All right. With that, we will now break for lunch. We will reconvene again in this room at 1:00 p.m. Please take any personal belongings you may want with you at this time. We could do 1:20 if the committee members would so prefer. Any preference?

Would the committee members prefer 1:00 or 1:20? 1:00?

We will reconvene at 1:00 p.m. Please take any personal belongings you may want with you at this time. The ballroom will be secured by FDA staff during the lunch break. Committee members, please remember that there should be no discussion of the meeting during lunch amongst yourselves, FDA, or with any member of the audience. Thank you.

(Whereupon, at 12:20 p.m., the morning session was adjourned.)